



PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : C07D 309/38, 309/32 A61K 31/365		A1	(11) International Publication Number: WO 94/11361 (43) International Publication Date: 26 May 1994 (26.05.94)
(21) International Application Number: PCT/US93/10645 (22) International Filing Date: 9 November 1993 (09.11.93) (30) Priority data: 07/975,343 13 November 1992 (13.11.92) US 08/090,876 13 July 1993 (13.07.93) US 08/130,641 1 October 1993 (01.10.93) US (60) Parent Applications or Grants (63) Related by Continuation US 07/975,343 (CIP) Filed on 13 November 1992 (13.11.92) US 08/090,876 (CIP) Filed on 13 July 1993 (13.07.93) US 08/130,641 (CIP) Filed on 1 October 1993 (01.10.93) (71) Applicant (for all designated States except US): THE UPJOHN COMPANY [US/US]; 301 Henrietta Street, Kalamazoo, MI 49001 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): THAISRVONGS, Suvit [US/US]; 5695 Swallow, Portage, MI 49002 (US). YANG, Chih-Ping [-/-]; 3F, #153, Kang-Ioh Street, Neihu, Taipei (TW). STROHBACH, Joseph, Walter [US/US]; 54490 M-66, Mendon, MI 49072 (US).		TURNER, Steven, Ronald [US/US]; 1713 Banbury Road, Kalamazoo, MI 49001 (US). ROMERO, Donna, Lee [US/US]; 2721 Lake Chevy Chase Drive, Kalamazoo, MI 49008 (US). SKALETZKI, Louis, L. [US/US]; 3731 Greenleaf Circle, Kalamazoo, MI 49008 (US). ARISTOFF, Paul, Adrian [US/US]; 1650 Brookmoor Lane, Kalamazoo, MI 49002 (US). GAMMILL, Ronald, B. [US/US]; 6704 Pleasantview Drive, Kalamazoo, MI 49002 (US). JOHNSON, Paul, D. [US/US]; 6960 Towhee, Portage, MI 49002 (US). SKULNICK, Harvey, Irving [US/US]; 1745 Old Deer Run, Kalamazoo, MI 49009 (US). PIPER, Richard, C. [US/US]; 5252 Birchwood Drive, Kalamazoo, MI 49009 (US). TOMMASI, Ruben, A. [US/US]; 1233 Banbury Road, Kalamazoo, MI 49001 (US). ZHANG, Qingwei [CN/US]; 550 Locust Street, Apt. #1, Kalamazoo, MI 49007 (US). (74) Agent: GAMMILL, Martha, A.; Corporate Intellectual Property Law, The Upjohn Company, 301 Henrietta Street, Kalamazoo, MI 49001 (US). (81) Designated States: AT, AU, BB, BG, BR, BY, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, UZ, VN, European patent: (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report.	
(54) Title: PYRAN-2-ONES AND 5,6-DIHYDROPYRAN-2-ONES USEFUL FOR TREATING HIV AND OTHER RETROVIRUSES			
<div style="text-align: center;"> </div> <div style="text-align: right;">(I)</div>			
(57) Abstract <p>The present invention relates to compounds of formula (I) which are pyran-2-ones and 5,6-dihydropyran-2-ones useful for inhibiting a retrovirus in a mammalian cell infected with said retrovirus.</p>			

BEST AVAILABLE COPY

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LJ	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TC	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

PYRAN-2-ONES AND 5,6-DIHYDROPYRAN-2-ONES USEFUL FOR
TREATING HIV AND OTHER RETROVIRUSES
FIELD OF THE INVENTION

The present invention relates to compounds useful for inhibiting a retrovirus in a human
5 cell infected with said retrovirus. More particularly, the present invention provides pyran-2-ones
and 5,6-dihydropyran-2-ones as HIV-proteinase inhibitors.

BACKGROUND OF THE INVENTION

During the past decade, acquired immunodeficiency syndrome (AIDS) has progressed
from having the status of a medical curiosity afflicting only a small number of individuals to a
10 problem of major proportions, both medically and economically. John Saunders and Richard
Storer, "New Developments in RT Inhibitors," DN&P 5(3), April 1992, pages 153-169. WHO
figures reveal that more than 360,000 cases of AIDS have been reported worldwide, including
nearly 175,000 cases in the U.S.A. Of these, approximately 100,00 worldwide (50,000 in the
U.S.A.) were reported in the preceding 12-month period. In the U.S.A., the number of
15 seropositive individuals is thought to be approximately two million, and estimates suggest that
5-10 million people worldwide may be seropositive. Saunders and Storer, page 153.

Since the first description of the malady in the early part of this decade, acquired
immunodeficiency disease syndrome (AIDS) and its devastating consequences have been
subjects of continuous and intense coverage in both the lay and scientific press. Indeed, an
20 edition of Scientific American was entirely devoted to AIDS (Scientific American 289, #4
(1988)), and the literature on the disease and the virus is already so vast as to defy thorough
citation.

On March 20, 1987, the FDA approved the use of the compound, zidovudine (AZT), to
treat AIDS patients with a recent initial episode of pneumocystis carinii pneumonia, AIDS
25 patients with conditions other than pneumocystis carinii pneumonia or patients infected with the
virus with an absolute CD4 lymphocyte count of less than $200/\text{mm}^3$ in the peripheral blood.
AZT is a known inhibitor of viral reverse transcriptase, an enzyme necessary for human
immunodeficiency virus replication. U.S. Patent 4,724,232 claims a method of treating humans
having acquired immunodeficiency syndrome utilizing 3'-azido-3'-deoxy-thymidine
30 (azidothymidine, AZT).

Following the discovery of the anti-HIV activity of AZT, much effort has been focused
on a wide variety of other dideoxynucleoside analogues in the search for superior agents. In the
case of the 2',3'-dideoxy series, ddC and ddI have shown potent activity against HIV *in vitro*
and have been evaluated in clinical trials. Saunders and Storer, page 160. The compound ddC
35 is currently being developed by Hoffman-La Roche Co. as a potential anti-AIDS drug. Its
limiting toxicity in humans is peripheral neuropathy which is reversible at low doses. Raymond

-2-

R. Schinazi, Jan R. Mead and Paul M. Feorino, "Insights Into HIV Chemotherapy," *Aids Research and Human Retroviruses*, Vol. 8, Number 6, 1992, pages 963-990. It has been approved by the FDA for AIDS therapy in combination with AZT. The compound ddI has also been evaluated in clinical trials. Its limiting toxicities are peripheral neuropathy and pancreatitis. It has also been shown to stimulate hepatic glycolysis leading to irreversible liver damage. Schinazi, Mead and Feorino, page 966. It has recently been approved by FDA for the treatment of HIV-1 infections in adults and pediatrics patients who are intolerant to or whose health has significantly deteriorated while on AZT treatment. Schinazi, Mead and Feorino, page 966.

Among these approved drugs, AZT is currently the only drug that has been shown to decrease the mortality and frequency of opportunistic infections associated with AIDS. Schinazi, Mead and Feorino, page 963.

Human immunodeficiency virus (HIV) has long been recognized as the causative agent in AIDS, although a minority opinion to the contrary has been expressed (e.g., P. Duesberg, *Proc. Natl. Acad. Sci., USA*, 86:755-764 (1989)). Sequence analysis of the complete genomes from several infective and non-infective HIV-isolates has shed considerable light on the make-up of the virus and the types of molecules that are essential for its replication and maturation to an infective species. The HIV protease is essential for the processing of the viral gag and gag-pol polypeptides into mature virion proteins. L. Ratner, et al., *Nature*, 313:277-284 (1985); L.H. Pearl and W.R. Taylor, *Nature*, 329:351 (1987). HIV exhibits the same gag/pol/env organization seen in other retroviruses. L. Ratner, et al., *Nature*, 313:277-284 (1985); S. Wain-Hobson, et al., *Cell*, 40:9-17 (1985); R. Sanchez-Pescador, et al., *Science*, 227:484-492 (1985); and M.A. Muesing, et al., *Nature*, 313: 450-458 (1985).

Reverse transcriptase (RT) is an enzyme unique to retroviruses that catalyzes the conversion of viral RNA into double stranded DNA. Blockage at any point during the transcription process, by AZT or any other aberrant deoxynucleoside triphosphate incapable of elongation, should have dramatic consequences relative to viral replication. Much work on the RT target is in progress based, in large measure, upon the fact that nucleosides like AZT are easily delivered to cells. However, the inefficiency of phosphorylation steps to the triphosphate, and the lack of specificity and consequent toxicity, constitute major drawbacks to use of AZT and similar nucleosides having a blocked, or missing, 3'hydroxyl group.

The T4 cell receptor for HIV, the so-called CD4 molecule, has also been targeted as an intervention point in AIDS therapy. R.A. Fisher, et al., *Nature*, 331:76-78 (1988); R.E. Hussey, et al., *Nature*, 331:78-81 (1988); and K.C. Deen, et al., *Nature*, 331:82-84 (1988). The exterior portion of this transmembrane protein, a molecule of 371 amino acids (sCD4) has been expressed in Chinese hamster ovary (CHO) cells and Genentech (D.H. Smith, et al., *Science*, 238:1704-1707 (1987)) has had a product in clinical trials since the fall of 1987. CD4 has been

shown to have a narrow spectrum of activity against wild-type virus and so far has failed to control HIV infection in humans. Schinazi, Mead and Feorino, page 963. The idea behind CD4 based therapy is that the molecules can neutralize HIV by interfering with viral attachment to T4, and other cells which express CD4 on their surfaces. A variant on this theme is to attach
5 cell toxins to CD4 for specific binding and delivery to infected cells which display glycoprotein gp-120 on their surfaces. M.A. Till, et al., Science, 242:1166-1168 (1988); and V.K. Chaudhary, et al., Nature, 335:369-372 (1988).

Another therapeutic target in AIDS involves inhibition of the viral protease (or proteinase) that is essential for processing HIV-fusion polypeptide precursors. In HIV and
10 several other retroviruses, the proteolytic maturation of the gag and gag/pol fusion polypeptides (a process indispensable for generation of infective viral particles) has been shown to be mediated by a protease that is, itself, encoded by the pol region of the viral genome. Y. Yoshinaka, et al., Proc. Natl. Acad. Sci. USA, 82:1618-1622 (1985); Y. Yoshinaka, et al., J. Virol., 55:870-873 (1985); Y. Yoshinaka, et al., J. Virol., 57:826-832 (1986); and K. von der
15 Helm, Proc. Natl. Acad. Sci., USA, 74:911-915 (1977). Inhibition of the protease has been shown to inhibit the processing of the HIV p55 in mammalian cell and HIV replication in T lymphocytes. T.J. McQuade, et al., Science, 247:454 (1990).

The protease (or proteinase), consisting of only 99 amino acids, is among the smallest enzymes known, and its demonstrated homology to aspartyl proteases such as pepsin and renin
20 (L.H. Pearl and W.R. Taylor, Nature, 329: 351-354 (1987); and I. Katoh, et al., Nature, 329:654-656 (1987)), led to inferences regarding the three-dimensional structure and mechanism of the enzyme (L.H. Pearl and W.R. Taylor, Nature, 329:351-354 (1987)) that have since been borne out experimentally. Active HIV protease has been expressed in bacteria (see, e.g., P.L. Darke, et al., J. Biol. Chem., 264:2307-2312 (1989)) and chemically synthesized (J. Schneider
25 and S.B. Kent, Cell, 54:363-368 (1988); and R.F. Nutt, et al., Proc. Natl. Acad. Sci., USA, 85:7129-7133 (1988)). Site directed mutagenesis (P.L. Darke, et al., J. Biol. Chem., 264: 2307-2312 (1989); and N.E. Kohl, et al., Proc. Natl. Acad. Sci., USA, 85:4686-4690 (1988)) and pepstatin inhibition (P.L. Darke, et al., J. Biol. Chem., 264:2307-2312 (1989); S. Seelmeier, et al., Proc. Natl. Acad. Sci., USA, 85:6612-6616 (1988); C.-Z. Giam and I. Borsos, J. Biol.
30 Chem., 263:14617-14720 (1988); and J. Hansen, et al., EMBO J., 7:1785-1791 (1988)) have provided evidence for HIV protease's mechanistic function as an aspartyl protease. A study has demonstrated that the protease cleaves at the sites expected in peptides modeled after the regions actually cleaved by the enzyme in the gag and pol precursor proteins during viral maturation. P.L. Darke, et al., Biochem. Biophys. Res. Commun., 156:297-303 (1988). X-ray crystal-
35 lographic analysis of the HIV-protease (M.A. Navia, et al., Nature, 337:615-620 (1989)) and a related retroviral enzyme from Rous sarcoma virus (M. Miller, et al., Nature, 337:576-579

(1989)) reveal an active site in the protease dimer that is identical to that seen in other aspartyl proteases, thus supporting the supposition (L.H. Pearl and W.R. Taylor, *Nature*, 329:351-354 (1987)) that the HIV enzyme is active as a dimer. See also Joseph A. Martin, "Recent Advances in the Design of HIV Proteinase Inhibitors," *Antiviral Research*, 17 (1992) 265-278.

5 To date, the scientific search for a fully effective and safe means of inhibiting retroviruses in a human hosting such a virus, and thereby effectively treating diseases caused by such a virus, such as acquired immunodeficiency syndrome (AIDS), continues.

It is well known in the art that certain undesirable physiological manifestations, such as acne vulgaris, seborrhea, female hirsutism, male pattern baldness and benign prostatic
10 hypertrophy, are the result of hyperandrogenic stimulation caused by an excessive accumulation of testosterone or related active hormones in the target tissues. U.S. Patent 4,377,584, col. 1, lines 18-24. Additionally, the reduction of androgen levels has been shown to have a therapeutic effect on prostate cancer. See, e.g., U.S. Patent 5,017,568, col. 2, lines 4-6.

It is also known in the art that the principal mediator of androgenic activity in some
15 target organs is 5α -dihydrotestosterone and related 5α -reduced androgens, and that it is formed locally in the target organ by the action of steroid- 5α -reductase. It therefore has been postulated and demonstrated that inhibitors of steroid- 5α -reductase will serve to prevent or lessen symptoms of hyperandrogenic stimulation. See, e.g., U.S. Patent 4,377,584, col. 1, lines 38-45.

Examples of compounds that are antiandrogens by virtue of their ability to inhibit
20 testosterone- 5α -reductase are disclosed in U.S. Patents 4,377,584; 4,760,071; and 5,017,568.

INFORMATION DISCLOSURE

JO 3227-923-A (Sawai Seiyaku KK) discloses the use of 4-hydroxy-coumarins as therapeutic agents for HIV-infected patients.

WO 91/04663 (Univ. of Calif. at Oakland) discloses 6-amino-1,2-benzopyrones which
25 are useful for treating viral diseases.

WO 91/12804 (Kabi Pharmaceutical) discloses the use of Linomide® for the treatment of retrovirus infections.

International Publication No. WO 89/07939, published 8 September 1989, discloses specific coumarin compounds which are reverse transcriptase inhibitors.

30 U.S. Patents Nos. 3,489,774 and 3,493,586 disclose 3-(beta-aryl-beta-(arylthio) (or aryl seleno) propionyl-coumarin and pyrone products useful as parasiticides.

Biochemical and Biophysical Research Communications, Vol. 188, No. 2, 1992, pages 631-637, discloses chromones bearing hydroxyl substituents and a phenolic group at the 2-position (flavones) as having anti-HIV-1 proteinase activity.

35 Antimicrobial Patent Fast-Alert, Week Ending 4 September 1992, disclose gamma-pyrones, gamma-pyridones and gamma-thio-pyrones as antiviral agents.

-5-

International Publication Nos. WO 92/04326, 92/04327 and 92/04328, all published 1992, disclose antiviral heterocyclic derivatives, such as quinolinones and isopyranones, as replication inhibitors for treating herpes simplex 1 and 2, cytomegalovirus and Epstein-Barr virus.

C.A. Selects: Antitumor Agents, Issue 19, 1992, page 25. No. 117: 90147q (PCT International Application WO 92 06,687) discloses the preparation of 5-iodo-5-amino-1,2-isopyranes and analogs as cytostatic and antiviral agents.

Nowhere do these references teach or suggest the use of 4-hydroxy- α -pyranones as HIV protease inhibitors or as having antiviral activity.

Phytochemistry, 31(3):953-956 (1992), discloses compounds, such as 4-hydroxy- α -(4-methoxyphenyl)-6-[2-(4-methoxyphenyl)ethenyl]-2-oxo-, methyl ester, (E)-(-)-2H-pyran-3-acetic acid.

Tetrahedron, 48(9):1695-1706 (1992), (see also Tetrahedron Lett., 30(23):3109-12 (1989)), discloses compounds, such as 3-[1-(4-chlorophenyl)-3-(4-nitrophenyl)-2-propenyl]-4-hydroxy-6-methyl-2H-pyran-2-one; 3-[3-(4-chlorophenyl)-1-(4-nitrophenyl)-2-propenyl]-4-hydroxy-6-methyl-2H-pyran-2-one; 4-hydroxy-3-[3-(4-methoxyphenyl)-1-(4-nitrophenyl)-2-propenyl]-6-methyl-2H-pyran-2-one; and 4-hydroxy-3-[1-(4-methoxyphenyl)-3-(4-nitrophenyl)-2-propenyl]-6-methyl-2H-pyran-2-one.

Tennen Yuki Kagobutsu Toronkai Koen Yoshishu, 30:17-24 (1988), discloses compounds, such as 4-hydroxy- β -(4-methoxyphenyl)-6-[2-(4-methoxyphenyl)ethenyl]-2-oxo-, methyl ester, (E)-(-)-2H-pyran-3-propanoic acid.

Chem. Absts. 53:15072f discloses compounds, such as α -1,3-dihydroxy-2-butenylidene- γ -butyrolactone, δ -lactone, hydrocinnamic acid.

Chem. Absts. 53:15072c discloses compounds, such as α -1,3-dihydroxy-2-butenylidene- γ -butyrolactone, δ -lactone, hydrocinnamic acid.

Arch. Pharm. (Weinheim, Ger.), 316(12):988-94 (1983), discloses compounds, such as 3-(4-chlorophenyl)-3-oxobutyl-4-hydroxy-6-methyl-2H-pyran-2-one; and 3-[1-(4-chlorophenyl)propyl]-4-hydroxy-6-methyl-2H-pyran-2-one.

Chem. Ber., 110(3):1047-57 (1977), discloses compounds, such as 6-(3,4-dimethoxyphenyl)-3-[2-(3,4-dimethoxyphenyl)-1-(4-methoxy-2-oxo-2H-pyran-6-yl)ethyl]-4-hydroxy-2H-pyran-2-one; and 3-[2-(3,4-dimethoxyphenyl)-1-(4-methoxy-2-oxo-2H-pyran-6-yl)ethyl]-4-hydroxy-6-[2-(4-methoxyphenyl)ethyl]-2H-pyran-2-one.

J. Heterocycl. Chem., 23(2):413-16 (1986), discloses compounds, such as 3-[(4-nitrophenyl)-1-piperidinylmethyl]-4-hydroxy-6-methyl-2H-pyran-2-one.

The following published PCT applications disclose peptides useful as retroviral protease inhibitors: International Publication No. WO 91/06561, published 16 May 1991; and

-6-

International Publication No. WO 92/17490, published 15 October 1992.

The following references disclose pyrone compounds which are believed to be representative of those known in the art:

EP-443449 (German language) discloses 3-hexyl-5,6-dihydro-6-pentyl-2H-pyran-2-one and 3-ethyl-6-hexadecyl-5,6-dihydro-4-hydroxy-2H-pyran-2-one. Pestic. Sci., 27(1):45-63 (1989), discloses 5,6-dihydro-4-hydroxy-6-methyl-6-(1-methyl-1-propenyl)-3-(1-oxobutyl)-2H-pyran-2-one; and 6-cyclopropyl-5,6-dihydro-4-hydroxy-6-methyl-3-(1-oxobutyl)-2H-pyran-2-one. Acta. Chem. Scand., 43(2):193-95 (1989), discloses 4-(acetyloxy)-5,6-dihydro-3,6-dimethyl-2H-pyran-2-one. J. Org. Chem., 54(14):3383-9 (1989), discloses 5,6-dihydro-4-hydroxy-3,6,6-dimethyl-2H-pyran-2-one. J. Org. Chem., 53(6):1218-21 (1988); and Tetrahedron Lett., 34(2):277-80 (1993), discloses 3-hexyldihydro-6-undecyl-2H-pyran-2,4 (3H)-dione, (6R)-. J. Chem. Soc. Perkins Trans., 1(6):1157-9 (1985), discloses dihydro-3-methyl-6-nonyl-6-methyl-2H-pyran-2-yl]oxy]methyl]-2H-pyran-2,4 (3H)-dione. J. Chem. Ecol., 9(6):703-14 (1983), discloses 5,6-dihydro-4-hydroxy-3,6-dimethyl-2H-pyran-2-one. J. Org. Chem., 48(7):1123-5 (1983), discloses 6-(2-chloro-1-methylethenyl)-5,6-dihydro-4-hydroxy-3-methyl-2H-pyran-2-one, (Z)-(+)-. Acta. Chem. Scand., 43(2):193-95 (1989); and Tetrahedron Lett., 31(6):551-4 (1980), discloses 5,6-dihydro-4-hydroxy-3,6-dimethyl-2H-pyran-2-one. Helv. Chim. Acta., 59(7):2393-2401 (1976), discloses 4-[(3,6-dihydro-4-hydroxy-5-methyl-6-oxo-2H-pyran-2-methyl]-2,6-piperidinedione. Acta. Chem. Scand., 30(7):613-18 (1976); and Tetrahedron Lett., 17:22:1903-4 (1976), discloses 5,6-dihydro-4-hydroxy-3-methyl-6-(1-methyl-1-propenyl)-2H-pyran-2-one, (E)-. 3,3'-[(4-nitrophenyl)methylene]bis[5,6-dihydro-4-hydroxy-6-methyl-2H-pyran-2-one; and 3,3'-(phenylmethylene)bis[5,6-dihydro-4-hydroxy-6-methyl-2H-pyran-2-one are disclosed in Synth. Commun., 20(18):2827-2836, 1990.

WO 93/07868, published 29 April 1993, discloses new nitroso-benzopyrone, -benzamide and -isoquinolinone derivatives as adenosine di-phosphoribose transferase inhibitors for treating viral infections and cancer.

WO 93/07128, published 15 April 1993, relates to substituted cyclic carbonyls and derivatives thereof useful as retroviral protease inhibitors.

J. Indian Chem. Soc., 69:397-398 (July 1992), discloses that coumarin-4-acetic acids were screened for their anticancer and anti-AIDS activities and were found to be inactive.

The Journal of Antibiotics, 46(7):1126 (July 1993), discloses germicidin, which is 6-(2-ethyl)-3-ethyl-4-hydroxy-2-pyrone, to be an autoregulative germination inhibitor of *Streptomyces tchouchromogenes* NRRL B-1551.

Derwent Abstracts, 93-168920/21 of EP 543201 discloses the use of coumarin derivatives, such as 1-(N-morpholyl)-6-(4-hydroxybenzoic acid ethyl ester) hexane, for the treatment of viral infections, such as influenza or acute rhinitis.

J. Org. Chem., 48(22):3945-7 (1983); and Chem. Pharm. Bull., 29(10):2762-8 (1981); disclose compounds such as 4-hydroxy-6-(3-pyridinyl)-2H-pyran-2-one.

J. Labelled Compd. Radiopharm., 28(10):1143-8 (1990), discloses compounds such as 4-hydroxy-6-methyl-2H-pyran-2-one.

5 J. Am. Chem. Soc., 113(25):9585-95 (1991), discloses compounds such as 3-(3-phenyl-2-propen-1-yl)-6-methyl-4-hydroxy-2H-pyran-2-one.

CA 54:14239d and CA 53:4272c disclose compounds such as α -(α , γ -dihydroxycinnamylidene)-, δ -lactone hydrocinnamic acid.

10 CA 53:15072f discloses compounds such as α -1,3-dihydroxy-2-butenylidene- β -ethyl-, δ -lactone hydrocinnamic acid.

Synth. Commun., 20(18):2827-36 (1990), discloses compounds such as 3,3'-[(4-nitrophenyl)methylene]bis[5,6-dihydro-4-hydroxy-6-methyl-2H-pyran-2-one, and 3,3'-(phenylmethylene)bis[5,6-dihydro-4-hydroxy-6-methyl-2H-pyran-2-one.

15 J. Org. Chem., 54(14):3383-9 (1989), discloses compounds such as 5,6-dihydro-4-hydroxy-3,6,6-trimethyl-2H-pyran-2-one.

Derwent Abstract, 92-166863/20, of EP 553248 discloses new optionally substituted 5-iodo-6-amino-1,2-benzopyrone derivatives, which are adenosine di:phospho-ribose inhibitors, for treatment and prevention of viruses and tumors associated with AIDS.

20 Finasteride [also named N(1,1-dimethylethyl)-3-oxo-4-aza-5 α -androst-1-ene, 17 β -carboxamide] (PROSCAR®) is a 5 α -reductase inhibitor which is used to reduce the prostate size in men. It has recently been approved by the FDA for the treatment of benign prostatic hyperplasia. Related patents are U.S. Patents 4,377,584 and 4,760,071, which disclose that 4-aza-17 β -substituted-5 α -androst-3-ones, specifically the compound 17 β -(N-t-butylcarbonyl)-4-aza-5 α -androst-1-en-3-one, and their A-homo analogs, are active as testosterone 5 α -reductase
25 inhibitors, and thus useful topically for treatment of acne, seborrhea, female hirsutism and systemically in treatment of benign prostatic hypertrophy. See also Journal of Andrology, 10:259-262 (1989); J. Steroid. Biochem. Molec. Biol., Vol. 44, No. 2, pp. 121-131 (1993).

U.S. Patent 5,017,568 discloses substituted acrylate analogues of steroidal synthetic compounds having 5 α -reductase inhibitor activity, and therefore useful in treating diseases, such
30 as acne vulgaris, seborrhea, female hirsutism, prostate diseases, such as benign prostatic hypertrophy and prostatic adenocarcinoma and male pattern baldness.

A selective, non-steroidal inhibitor of human steroid 5 α -reductase type 1 is LY 191704 [8-chloro-4-methyl-1,2,3,4,4 α ,5,6,10b-octahydro-benzo[f]quinolin-3(2H)-one], Proc. Natl. Acad. Sci. USA, Vol. 90:5277-5281 (1993).

35 SUMMARY OF THE INVENTION

The present invention particularly provides:

compound of the formula I

in R_1 is

- a) $-(CH_2)_n-CH(R_3)-(CH_2)_m-R_4$,
- b) $-CH(aryl)-CH[C(O)-O-C_1-C_6 \text{ alkyl}]_2$,
- c) $-C(C_3-C_5 \text{ cycloalkyl})-(CH_2)_n-R_4$,
- d) $-C(aryl)=CH-aryl$, or
- e) $-CH(R_3)-S-(CH_2)_m-R_4$;

in R_2 is

- a) hydrogen,
- b) halo,
- c) $C_1-C_6 \text{ alkyl}-[O-(CH_2)_2]_q-(CH_2)_n$, or
- d) $C_1-C_6 \text{ alkyl}$;

in R_3 is

- a) $C_2-C_{10} \text{ alkyl}$ optionally substituted by zero (0) to five (5) halo,
- b) $C_2-C_{10} \text{ alkenyl}$,
- c) $R_4-(CH_2)_m-CH(R_6)-(CH_2)_n$,
- d) $R_4-(CH_2)_p$,
- e) $R_4-CH=CH$,
- f) $CH_2=CH-(CH_2)_p$,
- g) $R_4(CH_2)_mX_1C(O)(CH_2)_n$,
- h) $R_4(CH_2)_mC(O)X_1(CH_2)_n$,
- i) aryl,
- j) het,
- k) $C_3-C_7 \text{ cycloalkyl}$,
- l) $C_1-C_6 \text{ alkyl}-O-C(O)-(CH_2)_n$,
- m) $C_1-C_6 \text{ alkyl}-[O-(CH_2)_2]_q-(CH_2)_n$,
- n) $R_4-CH(R_6)-CH(R_6)$,
- p) $R_{12}-(CH_2)_m-X_2-(CH_2)_n-(R_7)HC$, or
- q) $R_{15}-(CH_2)_m-X_2-(CH_2)_n-(R_7)HC$;

in R_4 is

- a) aryl,
- b) het,
- c) $C_3-C_7 \text{ cycloalkyl}$,
- d) $C_2-C_{10} \text{ alkenyl}$,
- e) $C_1-C_6 \text{ alkyl}-[O-(CH_2)_2]_q-(CH_2)_n$,
- f) halo,

-9-

- g) het-O-,
- h) het-C(O)-,
- i) aryl-(CH₂)_n-O-C(O)-, or
- j) trifluoromethyl;

5 wherein R₅ is

- a) C₁-C₁₀ alkyl,
- b) C₂-C₁₀ alkenyl,
- c) C₃-C₇ cycloalkyl,
- d) -(CH₂)_n-aryl,
- 10 e) -(CH₂)_p-het, or
- f) -(CH₂)_n-CH=CH-aryl;

wherein R₆ is

- a) C₁-C₁₀ alkyl,
- b) R₄-C₁-C₅ alkyl,
- 15 c) -(CH₂)_n-C₃-C₇ cycloalkyl,
- d) -(CH₂)_p-CH=CH₂,
- e) -(CH₂)_p-aryl,
- f) -(CH₂)_p-het, or
- g) hydroxy-;

20 wherein X₁ is -NR₇;

wherein R₇ is

- a) hydrogen, or
- b) C₁-C₅ alkyl;

wherein aryl is

- 25 a) phenyl substituted by zero (0) to three(3) R₈,
- b) naphthyl substituted by zero (0) to three(3) R₈,
- c) biphenyl substituted by zero (0) to three (3) R₈, or
- d) perhalophenyl;

30 wherein het is a 5- or 6-membered saturated or unsaturated ring containing from one (1) to four (4) heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring, C₃-C₈ cycloalkyl, or another heterocycle; and if chemically feasible, the nitrogen and sulfur atoms may be in the oxidized forms; and substituted by zero (0) to three (3) R₉;

wherein R₈ and R₉ are independently

- 35 a) C₁-C₈ alkyl substituted by zero (0) to three (3) halo,
- b) C₂-C₈ alkenyl,

- 5 c) hydroxy,
d) hydroxy-C₁-C₅ alkyl,
e) -(CH₂)_n-O-C₁-C₅ alkyl substituted by zero (0) to three (3) hydroxy,
f) -(CH₂)_n-O-C₂-C₇ alkenyl substituted by zero (0) to three (3) hydroxy,
g) halo,
h) amino,
i) amino-C₁-C₅ alkyl,
j) mono-or di-C₁-C₅ alkylamino,
k) -C(O)-C₁-C₅ alkyl,
10 l) -CHO,
m) -COOH,
n) -COOC₁-C₅alkyl,
o) -CON(R₇)₂,
p) C₃-C₇ cycloalkyl,
15 q) nitro,
r) -CN,
s) -SO₃H,
t) -SO₂NH₂,
u) -O[(CH₂)₂-O]_q-CH₃,
20 v) -[CH₂-O]_q-C₁-C₃ alkyl,
w) -(CH₂)_n-NHC(O)-O-(CH₂)_p-R₁₂,
x) -(CH₂)_n-NHC(O)-O-(CH₂)_p-R₁₅,
y) -(CH₂)_n-R₁₂,
z) -SO₂-R₁₂,
25 a1) -(CH₂)_n-X₂-(CH₂)_n-R₁₂,
b1) -(CH₂)_n-X₂-(CH₂)_n-R₁₅,
c1) -(CH₂)_n-X₂-CH=CH-R₁₂,
d1) -(CH₂)_n-X₂-CH=CH-R₁₅,
e1) -(CH₂)_n-X₂-C₁-C₁₀alkyl substituted by zero (0) to three (3) halo,
30 f1) -(CH₂)_n-X₂-C₂-C₅ alkenyl,
g1) -X₂-(CH₂)_p-CH(NH₂)(COOH),
h1) -NHCONH-SO₂-R₁₂,
i1) -X₂-(CH₂)_p-NH-C(O)-O-C₁-C₆ alkyl,
j1) -X₂-CH(X₃)-NH-C(O)-O-C₁-C₆ alkyl,
35 k1) -X₂-(CH₂)_p-CH[NH-C(O)-O-(CH₂)_p-R₁₂]-C(O)-O-(CH₂)_p-R₁₂,

- 5
 10
 11) $-(CH_2)_n-X_4-N(C_1-C_3 \text{ alkyl})_2$,
 m1) $-(CH_2)_n-X_4-NHR_{12}$,
 n1) $-NH-AA-P_1$,
 o1) $-(CH_2)_p-N_3$,
 p1) $-(CH_2)_p-R_{12}$,
 q1) $-(CH_2)_p-R_{15}$,
 r1) $-(CH_2)_n-NHC(SCH_3)=CHNO_2$,
 s1) $-(CH_2)_n-NHC(NHR_7)=CHNO_2$,
 t1) $-(CH_2)_n-NHC(SCH_3)=NCN$, or
 u1) $-(CH_2)_n-NHC(NHR_7)=NCN$;

wherein X_2 is

- 15
 a) $-NH-C(O)-$,
 b) $-NH-SO_2-$,
 c) $-NH-C(O)-NH-$, or
 d) $-SO_2-NH-$;

wherein X_3 is

- a) C_1-C_6 alkyl, or
 b) $-(CH_2)_p-R_{15}$;

wherein X_4 is

- 20
 a) $-NH-C(O)-$, or
 b) $-NH-SO_2-$;

wherein R_{10} is hydrogen;

wherein R_{11} is

- 25
 a) hydrogen,
 b) C_1-C_6 alkyl,
 c) $-(CH_2)_n$ -aryl,
 d) $-(CH_2)_n-C_3-C_7$ cycloalkyl, or
 e) $-(CH_2)_n$ -het;

or wherein R_{10} and R_{11} taken together form a double bond;

30 or wherein R_3 and R_{11} taken together form

- a) C_3-C_8 cycloalkyl substituted by zero (0) to three (3) hydroxy, $=N-OH$,
 $=O$ (oxo), or protected form thereof, or substituted at the α -position by R_{14} ; or
 b) a 5- or 6-membered saturated ring containing one (1) or two (2) oxygen

atoms;

35 wherein R_{12} is

- a) phenyl substituted by zero (0) to three (3) R_{13} , or

b) naphthyl substituted by zero (0) to three (3) R_{13} ;

wherein R_{13} is

- a) C_1-C_{10} alkyl substituted by zero (0) to three (3) halo,
- b) hydroxy,
- 5 c) hydroxy- C_1-C_5 alkyl,
- d) $-(CH_2)_n-O-C_1-C_5$ alkyl substituted by zero (0) to three (3) hydroxy or halo,
- e) $-(CH_2)_n-O-C_2-C_7$ alkenyl substituted by zero (0) to three (3) hydroxy or halo,
- 10 f) halo,
- g) amino,
- h) amino C_1-C_5 alkyl,
- i) mono-or di- C_1-C_5 alkylamino,
- j) $-C(O)-C_1-C_5$ alkyl,
- 15 k) $-CHO$,
- l) $-COOH$,
- m) $-CON(R_7)_2$,
- n) $-NHCOC_1-C_3$ alkyl,
- o) $-NHOH$,
- 20 p) nitro,
- q) $-CN$,
- r) $-(CH_2)_n$ -phenyl,
- s) $-COOC_1-C_5$ alkyl, or
- t) $-SO_2$ -phenyl substituted by zero (0) to three (3) C_1-C_5 alkyl,
- 25 u) $-(CH_2)_n-X_4$ -phenyl, or
- v) $-(CH_2)_n-N=N$ -phenyl substituted by zero (0) or one (1) $-N(C_1-C_3$ alkyl) $_2$;

wherein R_{14} is

- a) $-(CH_2)_n$ -aryl,
- 30 b) $-C_1-C_6$ alkyl, or
- c) $-(CH_2)_n-C_4-C_7$ cycloalkyl;

wherein R_{15} is a 5- or 6-membered saturated or unsaturated ring containing from one (1) to four (4) heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring, C_3-C_8 cycloalkyl, or another heterocycle; and substituted by zero (0) to three (3) R_{13} ;

wherein AA is an amino acid residue;

wherein P_1 is hydrogen or a nitrogen protecting group;

wherein m and n are independently zero (0) to five (5) inclusive;

wherein p is one (1) to five (5) inclusive;

5 wherein q is one (1) to five (5) inclusive; and

pharmaceutically acceptable salts thereof.

The present invention particularly provides such compounds when R_1 is $-(CH_2)_n-$
 $CH(R_5)-(CH_2)_m-R_4$, $-C(C_3-C_5\text{cycloalkyl})-(CH_2)_n-R_4$, or $-CH(R_5)-S-(CH_2)_m-R_4$, R_4 is aryl, het
 or C_3-C_7 cycloalkyl.

10 For example, the present invention provides the following compounds:

The compound of formula I

wherein R_1 is $-CH(R_5)-R_4$;

wherein R_2 is hydrogen;

wherein R_3 is

- 15 a) C_3-C_8 alkyl,
 b) $R_4-(CH_2)_m-CH(C_6)-$,
 c) $R_4-(CH_2)_p-$,
 d) $R_4-CH=CH-$,
 e) $CH_2=CH-(CH_2)_p-$,
 20 f) $R_4-NH-C(O)-CH_2-$.

wherein R_4 is aryl;

wherein R_5 is

- a) C_2-C_5 alkyl,
 b) C_2-C_5 alkenyl,
 25 c) cyclopropyl;

wherein R_6 is

- a) C_2-C_5 alkyl, or
 b) $R_4-C_1-C_2$ alkyl-;

wherein aryl is

- 30 a) phenyl substituted by zero (0) to three (3) R_8 , or
 b) naphthyl substituted by zero (0) to three (3) R_8 ;

wherein R_8 is

- a) halo, or
 b) C_1-C_3 alkoxy;

35 wherein R_{10} and R_{11} taken together form a double bond;

wherein m is one (1) to three (3) inclusive;

wherein p is one (1) to three (3) inclusive.

More particularly, the present invention provides the following compounds:

The compound of formula I

wherein R_1 is $-\text{CH}(R_5)-R_4$;

5 wherein R_2 is hydrogen;

wherein R_3 is

- a) $\text{C}_5\text{-C}_8$ alkyl,
- b) $R_4-(\text{CH}_2)_m-\text{CH}(R_6)-$,
- c) $R_4-(\text{CH}_2)_p-$,
- 10 d) $\text{CH}_2=\text{CH}-(\text{CH}_2)_p-$, or
- e) $R_4-\text{CH}=\text{CH}-$;

wherein R_4 is aryl;

wherein R_5 is

- a) ethyl,
- 15 b) ethenyl, or
- c) cyclopropyl;

wherein R_6 is

- a) ethyl, or
- b) $R_4-\text{CH}_2-$;

20 wherein aryl is

- a) phenyl substituted by zero (0) to three (3) R_8 , or
- b) naphthyl substituted by zero (0) to three (3) R_8 ;

wherein R_8 is

- a) halo, or
- 25 b) methoxy;

wherein R_{10} and R_{11} taken together form a double bond;

wherein m is one or two;

wherein p is two (2) or three (3).

The present invention also provides the following compounds:

30 The compound of formula I

wherein R_1 is

- a) $-(\text{CH}_2)_n-\text{CH}(R_5)-(\text{CH}_2)_m-R_4$,
- b) $-\text{CH}(\text{aryl})-\text{CH}[\text{C}(\text{O})-\text{O}-\text{C}_1\text{-C}_6 \text{ alkyl}]_2$, or
- c) $-\text{C}(\text{aryl})=\text{CH}-\text{aryl}$;

35 wherein R_2 is hydrogen;

wherein R_3 is

-15-

- a) C_2-C_4 alkyl,
- b) $R_4-(CH_2)_p$,
- c) aryl, or
- d) cyclohexyl;

5 wherein R_4 is

- a) aryl, or
- b) het;

wherein R_5 is

- a) ethyl,
- 10 b) ethenyl,
- c) cyclopropyl,
- d) $-(CH_2)_n$ -aryl, or
- e) $-(CH_2)_n$ -CH=CH-aryl;

wherein R_{10} is hydrogen;

15 wherein R_{11} is

- a) hydrogen,
- b) C_1-C_4 alkyl,
- c) $-(CH_2)_n$ -aryl, or
- d) cyclohexyl;

20 or wherein R_3 and R_{11} taken together form

- a) C_3-C_8 cycloalkyl substituted by zero (0) to three (3) hydroxy, =N-OH, carbonyl group, or protected form thereof, or substituted at the α -position by $-(CH_2)_n$ -aryl, or
- b) a 5- or 6-membered saturated ring containing one (1) or two (2) oxygen atoms;

25 wherein aryl is phenyl substituted by zero (0) to three (3) R_8 ;

wherein het is

- a) thiophenyl substituted by zero (0) to three (3) R_9 , or
- b) furanyl substituted by zero (0) to three (3) R_9 ;

wherein R_8 and R_9 are independently

- 30 a) nitro,
- b) hydroxy,
- c) methyl, or
- d) $-[CH_2-O]_q-C_1-C_3$ alkyl;

wherein m is zero (0);

35 wherein n is zero (0) to three (3), inclusive;

wherein p is one (1) to three (3), inclusive;

-16-

wherein q is two (2).

The compound of formula I

wherein R_1 is

- 5 a) $-(CH_2)_n-CH(R_5)-(CH_2)_m-R_4$, or
 b) $-C(C_3-C_5\text{cycloalkyl})-(CH_2)_n-R_4$;

wherein R_2 is

- a) hydrogen, or
 b) halo;

wherein R_3 is

- 10 a) $R_4-(CH_2)_m-CH(R_6)-(CH_2)_n$,
 b) $R_4-(CH_2)_p$,
 c) C_3-C_6 alkyl substituted by zero (0) to three (3) halo, or
 d) $R_4-CH(R_6)-CH(R_6)-$;

wherein R_4 is

- 15 a) aryl,
 b) het,
 c) C_3-C_5 cycloalkyl,
 d) $CH_2=CH-$
 e) $CH_3-[O-(CH_2)_2]_q-$
 20 f) halo,
 g) het-O-, or
 h) $aryl-(CH_2)_n-O-C(O)-$;

wherein R_5 is

- a) ethyl,
 25 b) cyclopropyl, or
 c) $-CH_2$ -aryl;

wherein R_6 is

- a) ethyl,
 b) propyl,
 30 c) $-CH_2$ -cyclopropyl,
 d) $-CH_2-CH=CH_2$,
 e) $-CH_2$ -aryl, or
 f) hydroxy;

wherein aryl is phenyl substituted by zero (0) to three (3) R_8 ;

35 wherein het substituted by zero (0) to three (3) R_9 is

- a) indolyl,

-17-

- b) tetrahydro-furanyl,
- c) thiophenyl,
- d) isoxazolyl,
- e) tetrahydro-furanyl,
- f) tetrahydro-pyranyl,
- g) furanyl,
- h) (1,3)dioxolanyl,
- i) pyridinyl,
- j) morpholinyl,
- k) piperidinyl,
- l) pyrrolidinyl, or
- m) pyrrolidinonyl.

wherein R_8 is

- a) $-X_2-(CH_2)_p-NH-C(O)-O-C_1-C_6$ alkyl,
- b) $-(CH_2)_n-X_2-(CH_2)_n-R_{12}$,
- c) $-(CH_2)_n-X_2-(CH_2)_n-R_{15}$,
- d) $-(CH_2)_n-NHC(O)-O-(CH_2)_p-R_{12}$,
- e) $-NH-C(O)-NH-SO_2-R_{12}$,
- f) $-X_2-CH(X_3)-NHC(O)-O-C_1-C_6$ alkyl,
- g) $-X_2-(CH_2)_p-CH[NH-C(O)-O-(CH_2)_p-R_{12}]-C(O)-O-(CH_2)_p-R_{12}$,
- h) $-X_2-(CH_2)_p-CH(NH_2)(COOH)$,
- i) C_1-C_5 alkyl substituted by zero (0) to three (3) halo,
- j) halo, or
- k) C_1-C_5 alkyloxy;

wherein R_9 is

- a) methyl,
- b) halo,
- c) $-(CH_2)_n-R_{12}$,
- d) $-SO_2-R_{12}$,

wherein X_2 is

- a) $-NH-C(O)-$, or
- b) $-NH-C(O)-NH-$;

wherein X_3 is

- a) C_1-C_6 alkyl, or
- b) $-(CH_2)_p-R_{15}$;

wherein R_{10} and R_{11} taken together form a double bond;

wherein R_{12} is phenyl substituted by zero (0) to three (3) R_{13} ;

wherein R_{13} is

- a) methoxy,
- b) halo,
- 5 c) $-\text{SO}_2$ -phenyl substituted by zero (0) or one (1) $\text{C}_1\text{-C}_5$ alkyl,
- d) $-\text{CN}$, or
- e) $\text{C}_1\text{-C}_5$ alkyl;

wherein R_{15} substituted by zero (0) or one (1) R_{13} is

- a) indolyl,
- 10 b) pyridyl,
- c) imidazolyl, or
- d) quinoliny;

wherein m is zero (0) to three (3), inclusive;

wherein n is zero (0) to two (2), inclusive;

15 wherein p is one (1) to three (3), inclusive;

wherein q is two (2) or three (3). The present invention particularly provides such compounds when R_1 is $-(\text{CH}_2)_n\text{-CH}(\text{R}_5)\text{-(CH}_2)_m\text{-R}_4$ or $-\text{C}(\text{C}_3\text{-C}_5\text{cycloalkyl})\text{-(CH}_2)_n\text{-R}_4$, R_4 is aryl, het or $\text{C}_3\text{-C}_5$ cycloalkyl.

The compound of formula I

20 wherein R_1 is $-(\text{CH}_2)_n\text{-CH}(\text{R}_5)\text{-(CH}_2)_m\text{-R}_4$;

wherein R_2 is hydrogen;

wherein R_3 is $\text{R}_4\text{-(CH}_2)_m\text{-CH}(\text{R}_6)\text{-(CH}_2)_n$;

wherein R_4 is

- a) aryl, or
- 25 b) het;

wherein R_5 is $\text{C}_3\text{-C}_7$ cycloalkyl;

wherein R_6 is

- a) $\text{C}_1\text{-C}_{10}$ alkyl, or
- b) $-(\text{CH}_2)_n\text{-C}_3\text{-C}_7$ cycloalkyl;

30 wherein aryl is phenyl substituted by zero (0) or one (1) R_8 ;

wherein het is a 5- or 6-membered saturated or unsaturated ring containing from one (1) to four (4) heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring, $\text{C}_3\text{-C}_8$ cycloalkyl, or another heterocycle;

35 wherein R_8 is

- a) $-(\text{CH}_2)_n\text{-X}_2\text{-CH=CH-R}_{12}$.

-19-

- b) $-(CH_2)_n-X_2-(CH_2)_n-R_{12}$,
- c) $-(CH_2)_n-X_2-(CH_2)_n-R_{15}$,
- d) $-(CH_2)_n-X_2-C_1-C_{10}$ alkyl substituted by zero (0) or one (1) halo,
- e) $-(CH_2)_n-X_2-C_2-C_5$ alkenyl,
- f) $-(CH_2)_n-X_4-N(CH_3)_2$, or
- g) $-(CH_2)_n-X_4-NH-R_{12}$;

wherein X_2 is $-NHSO_2-$;

wherein X_4 is $-NHSO_2-$;

wherein R_{10} and R_{11} taken together form a double bond;

wherein R_{12} is

- a) phenyl substituted by zero (0) to three (3) R_{13} ,
- b) naphthyl substituted by zero (0) to three (3) R_{13} , or
- c) perhalophenyl;

wherein R_{13} is

- a) C_1-C_{10} alkyl substituted by zero (0) to three (3) halo,
- b) halo,
- c) $-O-C_1-C_5$ alkyl substituted by zero (0) to three (3) halo,
- d) $-CN$,
- e) nitro,
- f) $-COOH$,
- g) $-N(CH_3)_2$,
- h) hydroxy,
- i) $-NHCOCH_3$,
- j) amino,
- k) $-NHOH$,
- l) $-CONH_2$,
- m) $-CH_2NHCO$ -phenyl,
- n) $-SO_2$ -phenyl,
- o) $-N=N$ -phenyl substituted by zero (0) or one (1) $-N(CH_3)_2$, or
- p) $-NHSO_2$ -phenyl;

wherein R_{15} is a 5- or 6-membered saturated or unsaturated ring containing from one (1) to four (4) heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring, C_3-C_8 cycloalkyl, or another heterocycle, and substituted by zero (0) to two (2)

R_{13} ;

wherein m is zero (0) or one (1);

wherein n is zero (0) or one (1). The present invention particularly provides such compounds

wherein R_5 is cyclopropyl;

wherein R_6 is $-(CH_2)_n$ -cyclopropyl or ethyl;

5 wherein het is tetrahydropyranyl; and

wherein R_{15} substituted by zero (0) to two (2) R_{13} is

- a) phthalimidyl,
- b) quinoliny,
- c) thiophenyl,
- 10 d) pyridyl,
- e) isoxazolyl,
- f) thiophenyl,
- g) imidazolyl,
- h) benzo[1,2,5]oxadiazolyl,
- 15 i) benzo[1,2,5]thiadiazolyl, or
- j) 2-(isoxazol-3-yl)-thiophenyl.

The compound of formula I

wherein R_1 is

- a) $-(CH_2)_n-CH(R_5)-(CH_2)_m-R_4$, or
- 20 b) $-CH(R_5)-S-(CH_2)_m-R_4$;

wherein R_2 is

- a) hydrogen, or
- b) $-C_1-C_6$ alkyl;

wherein R_3 is

- 25 a) $R_4-(CH_2)_m-CH(R_6)-(CH_2)_n$,
- b) $R_4-CH(R_6)-CH(R_6)$,
- c) $R_{12}-(CH_2)_m-X_2-(CH_2)_n-(R_7)HC$ -, or
- d) $R_{15}-(CH_2)_m-X_2-(CH_2)_n-(R_7)HC$;

wherein R_4 is

- 30 a) aryl, or
- b) het;

wherein R_5 is

- a) C_1-C_4 alkyl, or
- b) cyclopropyl;

35 wherein R_6 is

- a) C_1-C_4 alkyl,

-21-

- b) $-\text{CH}_2\text{-cyclopropyl}$, or
- c) hydroxy;

wherein R_7 is

- a) hydrogen, or
- b) $\text{C}_1\text{-C}_5$ alkyl;

wherein aryl is phenyl substituted by zero (0) or two (2) R_8 ;

wherein het is

- a) furan-2-yl substituted by zero (0) or two (2) R_9 ,
- b) furan-3-yl substituted by zero (0) or two (2) R_9 ,
- c) thiophen-2-yl substituted by zero (0) or two (2) R_9 ,
- d) thiophen-3-yl substituted by zero (0) or two (2) R_9 ,
- e) tetrahydrofuran-2-yl substituted by zero (0) or two (2) R_9 ,
- f) tetrahydrofuran-3-yl substituted by zero (0) or two (2) R_9 ,
- g) tetrahydropyran-2-yl substituted by zero (0) or two (2) R_9 ,
- h) tetrahydropyran-3-yl substituted by zero (0) or two (2) R_9 , or
- i) 8-quinoliny;

wherein R_8 and R_9 are independently

- a) $\text{C}_1\text{-C}_8$ alkyl,
- b) halo,
- c) hydroxy- $\text{C}_1\text{-C}_4$ alkyl,
- d) $-(\text{CH}_2)_n\text{-X}_2\text{-(CH}_2)_n\text{-R}_{12}$,
- e) $-(\text{CH}_2)_n\text{-X}_2\text{-(CH}_2)_n\text{-R}_{15}$;

wherein X_2 is

- a) $-\text{NHSO}_2\text{-}$,
- b) $-\text{SO}_2\text{NH-}$, or
- c) $-\text{NHC(O)-}$;

wherein R_{10} and R_{11} taken together form a double bond;

wherein R_{12} is phenyl substituted by zero (0) to three (3) R_{13} ;

wherein R_{13} is

- a) $\text{C}_1\text{-C}_6$ alkyl,
- b) hydroxy,
- c) hydroxy- $\text{C}_1\text{-C}_5$ alkyl,
- d) halo,
- e) $-\text{CN}$, or
- f) amino;

wherein R_{15} is

-22-

- a) thiophen-2-yl substituted by zero (0) to three (3) R_{13} ,
- b) thiophen-3-yl substituted by zero (0) to three (3) R_{13} ,
- c) quinolin-8-yl substituted by zero (0) to three (3) R_{13} ,
- d) furan-2-yl substituted by zero (0) to three (3) R_{13} , or
- e) furan-3-yl substituted by zero (0) to three (3) R_{13} ;

wherein m is zero (0) to four (4), inclusive;

wherein n is zero (0) to four (4), inclusive.

Also the present invention provides:

A method of inhibiting a retrovirus in a mammalian cell infected with said retrovirus

10 which comprises treating said cell with an effective amount of a compound of the formula I

wherein R_1 is

- a) $-(CH_2)_n-CH(R_3)-(CH_2)_m-R_4$,
- b) $-CH(aryl)-CH[C(O)-O-C_1-C_6 \text{ alkyl}]_2$,
- c) $-C(C_3-C_5 \text{ cycloalkyl})-(CH_2)_n-R_4$,
- d) $-C(aryl)=CH-aryl$,
- e) $-CH(R_3)-S-(CH_2)_m-R_4$, or
- f) $-(CH_2)_p-aryl$;

wherein R_2 is

- a) hydrogen,
- b) halo,
- c) $C_1-C_6 \text{ alkyl}-[O-(CH_2)_2]_q-(CH_2)_n-$,
- d) $C_1-C_6 \text{ alkyl}$, or
- e) $-(CH_2)_n-CH(R_3)-(CH_2)_m-R_4$;

wherein R_3 is

- a) $C_1-C_{10} \text{ alkyl}$ optionally substituted by zero (0) to five (5) halo,
- b) $C_2-C_{10} \text{ alkenyl}$,
- c) $R_4-(CH_2)_m-CH(R_6)-(CH_2)_n-$,
- d) $R_4-(CH_2)_p-$,
- e) $R_4-CH=CH-$,
- f) $CH_2=CH-(CH_2)_p-$,
- g) $R_4(CH_2)_mX_1C(O)(CH_2)_n-$,
- h) $R_4(CH_2)_mC(O)X_1(CH_2)_n-$,
- i) aryl,
- j) het,
- k) $C_3-C_7 \text{ cycloalkyl}$,
- l) $C_1-C_6 \text{ alkyl}-O-C(O)-(CH_2)_n-$,

- m) C_1-C_6 alkyl- $[O-(CH_2)_2]_q-(CH_2)_n$;
- n) $R_4-CH(R_6)-CH(R_6)-$;
- p) $R_{12}-(CH_2)_m-X_2-(CH_2)_n-(R_7)HC-$, or
- q) $R_{15}-(CH_2)_m-X_2-(CH_2)_n-(R_7)HC-$;

5 wherein R_4 is

- a) aryl,
- b) het,
- c) C_3-C_7 cycloalkyl,
- d) C_2-C_{10} alkenyl,
- 10 e) C_1-C_6 alkyl- $[O-(CH_2)_2]_q-(CH_2)_n$,
- f) halo,
- g) het-O-
- h) het-C(O)-,
- i) aryl- $(CH_2)_n-O-C(O)-$, or
- 15 j) trifluoromethyl;

wherein R_5 is

- a) C_1-C_{10} alkyl,
- b) C_2-C_{10} alkenyl,
- c) C_3-C_7 cycloalkyl,
- 20 d) $-(CH_2)_n$ -aryl,
- e) $-(CH_2)_p$ -het, or
- f) $-(CH_2)_n-CH=CH$ -aryl;

wherein R_6 is

- a) C_1-C_{10} alkyl,
- 25 b) $R_4-C_1-C_5$ alkyl,
- c) $-(CH_2)_n-C_3-C_7$ cycloalkyl,
- d) $-(CH_2)_p-CH=CH_2$,
- e) $-(CH_2)_p$ -aryl,
- f) $-(CH_2)_p$ -het, or
- 30 g) hydroxy-

wherein X_1 is $-NR_7$;

wherein R_7 is

- a) hydrogen, or
- b) C_1-C_5 alkyl;

35 wherein aryl is

- a) phenyl substituted by zero (0) to three(3) R_8 .

-24-

- b) naphthyl substituted by zero (0) to three (3) R_8 ,
- c) biphenyl substituted by zero (0) to three (3) R_8 , or
- d) perhalophenyl;

wherein het is a 5- or 6-membered saturated or unsaturated ring containing from one (1) to four (4) heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring, C_3 - C_8 cycloalkyl, or another heterocycle; and if chemically feasible, the nitrogen and sulfur atoms may be in the oxidized forms; and substituted by zero (0) to three (3) R_9 ;

wherein R_8 and R_9 are independently

- 10 a) C_1 - C_8 alkyl substituted by zero (0) to three (3) halo,
- b) C_2 - C_8 alkenyl,
- c) hydroxy,
- d) hydroxy- C_1 - C_5 alkyl,
- e) $-(CH_2)_n-O-C_1-C_5$ alkyl substituted by zero (0) to three (3) hydroxy,
- 15 f) $-(CH_2)_n-O-C_2-C_7$ alkenyl substituted by zero (0) to three (3) hydroxy,
- g) halo,
- h) amino,
- i) amino- C_1 - C_5 alkyl,
- j) mono-or di- C_1 - C_5 alkylamino,
- 20 k) $-C(O)-C_1-C_5$ alkyl,
- l) $-CHO$,
- m) $-COOH$,
- n) $-COOC_1-C_5$ alkyl,
- o) $-CON(R_7)_2$,
- 25 p) C_3 - C_7 cycloalkyl,
- q) nitro,
- r) $-CN$,
- s) $-SO_3H$,
- t) $-SO_2NH_2$,
- 30 u) $-O[(CH_2)_2-O]_q-CH_3$,
- v) $-[CH_2-O]_q-C_1-C_3$ alkyl,
- w) $-(CH_2)_n-NHC(O)-O-(CH_2)_p-R_{12}$,
- x) $-(CH_2)_n-NHC(O)-O-(CH_2)_p-R_{15}$,
- y) $-(CH_2)_n-R_{12}$,
- 35 z) $-SO_2-R_{12}$,
- a1) $-(CH_2)_n-X_2-(CH_2)_n-R_{12}$,

-25-

- 5
- b1) $-(CH_2)_n \cdot X_2 \cdot (CH_2)_n \cdot R_{15}$,
 c1) $-(CH_2)_n \cdot X_2 \cdot CH=CH \cdot R_{12}$,
 d1) $-(CH_2)_n \cdot X_2 \cdot CH=CH \cdot R_{15}$,
 e1) $-(CH_2)_n \cdot X_2 \cdot C_1 \cdot C_{10}$ alkyl substituted by zero (0) to three (3) halo,
 f1) $-(CH_2)_n \cdot X_2 \cdot C_2 \cdot C_5$ alkenyl,
 g1) $-X_2 \cdot (CH_2)_p \cdot CH(NH_2)(COOH)$,
 h1) $-NHCONH \cdot SO_2 \cdot R_{12}$,
 i1) $-X_2 \cdot (CH_2)_p \cdot NH \cdot C(O) \cdot O \cdot C_1 \cdot C_6$ alkyl,
 j1) $-X_2 \cdot CH(X_3) \cdot NH \cdot C(O) \cdot O \cdot C_1 \cdot C_6$ alkyl,
 10 k1) $-X_2 \cdot (CH_2)_p \cdot CH[NH \cdot C(O) \cdot O \cdot (CH_2)_p \cdot R_{12}] \cdot C(O) \cdot O \cdot (CH_2)_p \cdot R_{12}$,
 l1) $-(CH_2)_n \cdot X_4 \cdot N(C_1 \cdot C_3 \text{ alkyl})_2$,
 m1) $-(CH_2)_n \cdot X_4 \cdot NHR_{12}$,
 n1) $-NH \cdot AA \cdot P_1$,
 o1) $-(CH_2)_p \cdot N_3$,
 15 p1) $-(CH_2)_p \cdot R_{12}$,
 q1) $-(CH_2)_p \cdot R_{15}$,
 r1) $-(CH_2)_n \cdot NHC(SCH_3)=CHNO_2$,
 s1) $-(CH_2)_n \cdot NHC(NHR_7)=CHNO_2$,
 t1) $-(CH_2)_n \cdot NHC(SCH_3)=NCN$, or
 20 u1) $-(CH_2)_n \cdot NHC(NHR_7)=NCN$;

wherein X_2 is

- a) $-NH \cdot C(O) \cdot$,
 b) $-NH \cdot SO_2 \cdot$,
 c) $-NH \cdot C(O) \cdot NH \cdot$, or
 25 d) $-SO_2 \cdot NH \cdot$;

wherein X_3 is

- a) $C_1 \cdot C_6$ alkyl, or
 b) $-(CH_2)_p \cdot R_{15}$;

wherein X_4 is

- 30 a) $-NH \cdot C(O) \cdot$, or
 b) $-NH \cdot SO_2 \cdot$;

wherein R_{10} is hydrogen;wherein R_{11} is

- a) hydrogen,
 35 b) $C_1 \cdot C_6$ alkyl,
 c) $-(CH_2)_n \cdot$ aryl,

-26-

d) $-(CH_2)_n-C_3-C_7$ cycloalkyl, ore) $-(CH_2)_n$ -het;or wherein R_{10} and R_{11} taken together form a double bond;or wherein R_3 and R_{11} taken together forma) C_3-C_8 cycloalkyl substituted by zero (0) to three (3) hydroxy, $=N-OH$, $=O$ (oxo), or protected form thereof, or substituted at the α -position by R_{14} ; or

b) a 5- or 6-membered saturated ring containing one (1) or two (2) oxygen

atoms;

wherein R_{12} isa) phenyl substituted by zero (0) to three (3) R_{13} , orb) naphthyl substituted by zero (0) to three (3) R_{13} ;wherein R_{13} isa) C_1-C_{10} alkyl substituted by zero (0) to three (3) halo,

b) hydroxy,

c) hydroxy- C_1-C_5 alkyl,d) $-(CH_2)_n-O-C_1-C_5$ alkyl substituted by zero (0) to three (3) hydroxy or

halo,

e) $-(CH_2)_n-O-C_2-C_7$ alkenyl substituted by zero (0) to three (3) hydroxy or

halo,

f) halo,

g) amino,

h) amino C_1-C_5 alkyl,i) mono-or di- C_1-C_5 alkylamino,j) $-C(O)-C_1-C_5$ alkyl,k) $-CHO$,l) $-COOH$,m) $-CON(R_7)_2$,n) $-NHCOC_1-C_3$ alkyl,o) $-NHOH$,

p) nitro,

q) $-CN$,r) $-(CH_2)_n$ -phenyl,s) $-COOC_1-C_5$ alkyl, ort) $-SO_2$ -phenyl substituted by zero (0) to three (3) C_1-C_5 alkyl,u) $-(CH_2)_n-X_4$ -phenyl, orv) $-(CH_2)_n-N=N$ -phenyl substituted by zero (0) or one (1) $-N(C_1-C_3$

alkyl)₂;

wherein R₁₄ is

- a) $-(CH_2)_n$ -aryl,
- b) $-C_1-C_6$ alkyl, or
- c) $-(CH_2)_n-C_4-C_7$ cycloalkyl;

wherein R₁₅ is a 5- or 6-membered saturated or unsaturated ring containing from one (1) to four (4) heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring, C₃-C₈ cycloalkyl, or another heterocycle; and substituted by zero (0) to three (3)

) R₁₃;

wherein AA is an amino acid residue;

wherein P₁ is hydrogen or a nitrogen protecting group;

wherein m and n are independently zero (0) to five (5) inclusive;

wherein p is one (1) to five (5) inclusive;

wherein q is one (1) to five (5) inclusive; and

pharmaceutically acceptable salts thereof.

For example, the present invention provides such method for compounds of the formula

I

wherein R₁ is $-CH(R_5)-R_4$;

wherein R₂ is hydrogen;

wherein R₃ is

- a) C₃-C₈ alkyl,
- b) $R_4-(CH_2)_m-CH(C_6)-$,
- c) $R_4-(CH_2)_p-$,
- d) $R_4-CH=CH-$,
- e) $CH_2=CH-(CH_2)_p-$,
- f) $R_4-NH-C(O)-CH_2-$,

wherein R₄ is aryl;

wherein R₅ is

- a) C₂-C₅ alkyl,
- b) C₂-C₅ alkenyl,
- c) cyclopropyl;

wherein R₆ is

- a) C₂-C₅ alkyl, or
- b) $R_4-C_1-C_2$ alkyl-;

wherein aryl is

-28-

- a) phenyl substituted by zero (0) to three (3) R_8 , or
- b) naphthyl substituted by zero (0) to three (3) R_8 ;

wherein R_8 is

- a) halo, or
- b) C_1 - C_3 alkoxy;

wherein R_{10} and R_{11} taken together form a double bond;

wherein m is one (1) to three (3) inclusive;

wherein p is one (1) to three (3) inclusive.

Also the present invention provides:

- 10 A method of preventing or treating benign prostatic hypertrophy or hyperplasia, prostatic cancer, alopecia, hirsutism, acne vulgaris and seborrhea comprising administering to a mammal in need of such prevention or treatment an effective amount of a compound of formula I

wherein R_1 is

- a) $-(CH_2)_n-CH(R_5)-(CH_2)_m-R_4$,
- 15 b) $-CH(aryl)-CH[C(O)-O-C_1-C_6 \text{ alkyl}]_2$,
- c) $-C(C_3-C_5 \text{ cycloalkyl})-(CH_2)_n-R_4$,
- d) $-C(aryl)=CH-aryl$,
- e) $-CH(R_5)-S-(CH_2)_m-R_4$, or
- f) $-(CH_2)_p-aryl$;

20 wherein R_2 is

- a) hydrogen,
- b) halo,
- c) $C_1-C_6 \text{ alkyl}-[O-(CH_2)_2]_q-(CH_2)_n$,
- d) $C_1-C_6 \text{ alkyl}$, or
- 25 e) $-(CH_2)_n-CH(R_5)-(CH_2)_m-R_4$;

wherein R_3 is

- a) $C_1-C_{10} \text{ alkyl}$ optionally substituted by zero (0) to five (5) halo,
- b) $C_2-C_{10} \text{ alkenyl}$,
- c) $R_4-(CH_2)_m-CH(R_6)-(CH_2)_n$,
- 30 d) $R_4-(CH_2)_p$,
- e) $R_4-CH=CH$,
- f) $CH_2=CH-(CH_2)_p$,
- g) $R_4(CH_2)_mX_1C(O)(CH_2)_n$,
- h) $R_4(CH_2)_mC(O)X_1(CH_2)_n$,
- 35 i) aryl,
- j) het,

-29-

- k) C_3-C_7 cycloalkyl,
- l) C_1-C_6 alkyl- $O-C(O)-(CH_2)_n-$,
- m) C_1-C_6 alkyl- $[O-(CH_2)_2]_q-(CH_2)_n-$,
- n) $R_4-CH(R_6)-CH(R_6)-$,
- 5 p) $R_{12}-(CH_2)_m-X_2-(CH_2)_n-(R_7)HC-$, or
- q) $R_{15}-(CH_2)_m-X_2-(CH_2)_n-(R_7)HC-$;

wherein R_4 is

- a) aryl,
- b) het,
- 10 c) C_3-C_7 cycloalkyl,
- d) C_2-C_{10} alkenyl,
- e) C_1-C_6 alkyl- $[O-(CH_2)_2]_q-(CH_2)_n-$,
- f) halo,
- g) het-O-,
- 15 h) het-C(O)-,
- i) aryl- $(CH_2)_n-O-C(O)-$, or
- j) trifluoromethyl;

wherein R_5 is

- a) C_1-C_{10} alkyl,
- 20 b) C_2-C_{10} alkenyl,
- c) C_3-C_7 cycloalkyl,
- d) $-(CH_2)_n$ -aryl,
- e) $-(CH_2)_p$ -het, or
- f) $-(CH_2)_n-CH=CH$ -aryl;

25 wherein R_6 is

- a) C_1-C_{10} alkyl,
- b) $R_4-C_1-C_5$ alkyl,
- c) $-(CH_2)_n-C_3-C_7$ cycloalkyl,
- d) $-(CH_2)_p-CH=CH_2$,
- 30 e) $-(CH_2)_p$ -aryl,
- f) $-(CH_2)_p$ -het, or
- g) hydroxy-;

wherein X_1 is $-NR_7-$;wherein R_7 is

- 35 a) hydrogen, or
- b) C_1-C_5 alkyl;

wherein aryl is

- a) phenyl substituted by zero (0) to three (3) R_8 ,
- b) naphthyl substituted by zero (0) to three (3) R_8 ,
- c) biphenyl substituted by zero (0) to three (3) R_8 , or
- 5 d) perhalophenyl;

wherein het is a 5- or 6-membered saturated or unsaturated ring containing from one (1) to four (4) heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring, C_3 - C_8 cycloalkyl, or another heterocycle; and if chemically feasible, the nitrogen and
 10 sulfur atoms may be in the oxidized forms; and substituted by zero (0) to three (3) R_9 ;
 wherein R_8 and R_9 are independently

- a) C_1 - C_8 alkyl substituted by zero (0) to three (3) halo,
- b) C_2 - C_8 alkenyl,
- c) hydroxy,
- 15 d) hydroxy- C_1 - C_5 alkyl,
- e) $-(CH_2)_n-O-C_1-C_5$ alkyl substituted by zero (0) to three (3) hydroxy,
- f) $-(CH_2)_n-O-C_2-C_7$ alkenyl substituted by zero (0) to three (3) hydroxy,
- g) halo,
- h) amino,
- 20 i) amino- C_1 - C_5 alkyl,
- j) mono-or di- C_1 - C_5 alkylamino,
- k) $-C(O)-C_1-C_5$ alkyl,
- l) $-CHO$,
- m) $-COOH$,
- 25 n) $-COOC_1-C_5$ alkyl,
- o) $-CON(R_7)_2$,
- p) C_3 - C_7 cycloalkyl,
- q) nitro,
- r) $-CN$,
- 30 s) $-SO_3H$,
- t) $-SO_2NH_2$,
- u) $-O[(CH_2)_2-O]_q-CH_3$,
- v) $-[CH_2-O]_q-C_1-C_3$ alkyl,
- w) $-(CH_2)_n-NHC(O)-O-(CH_2)_p-R_{12}$,
- 35 x) $-(CH_2)_n-NHC(O)-O-(CH_2)_p-R_{15}$,
- y) $-(CH_2)_n-R_{12}$,

-31-

- z) $-\text{SO}_2-\text{R}_{12}$,
 a1) $-(\text{CH}_2)_n-\text{X}_2-(\text{CH}_2)_n-\text{R}_{12}$,
 b1) $-(\text{CH}_2)_n-\text{X}_2-(\text{CH}_2)_n-\text{R}_{15}$,
 c1) $-(\text{CH}_2)_n-\text{X}_2-\text{CH}=\text{CH}-\text{R}_{12}$,
 5 d1) $-(\text{CH}_2)_n-\text{X}_2-\text{CH}=\text{CH}-\text{R}_{15}$,
 e1) $-(\text{CH}_2)_n-\text{X}_2-\text{C}_1-\text{C}_{10}\text{alkyl}$ substituted by zero (0) to three (3) halo,
 f1) $-(\text{CH}_2)_n-\text{X}_2-\text{C}_2-\text{C}_5$ alkenyl,
 g1) $-\text{X}_2-(\text{CH}_2)_p-\text{CH}(\text{NH}_2)(\text{COOH})$,
 h1) $-\text{NHCONH}-\text{SO}_2-\text{R}_{12}$,
 10 i1) $-\text{X}_2-(\text{CH}_2)_p-\text{NH}-\text{C}(\text{O})-\text{O}-\text{C}_1-\text{C}_6$ alkyl,
 j1) $-\text{X}_2-\text{CH}(\text{X}_3)-\text{NH}-\text{C}(\text{O})-\text{O}-\text{C}_1-\text{C}_6$ alkyl,
 k1) $-\text{X}_2-(\text{CH}_2)_p-\text{CH}[\text{NH}-\text{C}(\text{O})-\text{O}-(\text{CH}_2)_p-\text{R}_{12}]-\text{C}(\text{O})-\text{O}-(\text{CH}_2)_p-\text{R}_{12}$,
 l1) $-(\text{CH}_2)_n-\text{X}_4-\text{N}(\text{C}_1-\text{C}_3 \text{ alkyl})_2$,
 m1) $-(\text{CH}_2)_n-\text{X}_4-\text{NHR}_{12}$,
 15 n1) $-\text{NH}-\text{AA}-\text{P}_1$,
 o1) $-(\text{CH}_2)_p-\text{N}_3$,
 p1) $-(\text{CH}_2)_p-\text{R}_{12}$,
 q1) $-(\text{CH}_2)_p-\text{R}_{15}$,
 r1) $-(\text{CH}_2)_n-\text{NHC}(\text{SCH}_3)=\text{CHNO}_2$,
 20 s1) $-(\text{CH}_2)_n-\text{NHC}(\text{NHR}_7)=\text{CHNO}_2$,
 t1) $-(\text{CH}_2)_n-\text{NHC}(\text{SCH}_3)=\text{NCN}$, or
 u1) $-(\text{CH}_2)_n-\text{NHC}(\text{NHR}_7)=\text{NCN}$;

wherein X_2 is

- a) $-\text{NH}-\text{C}(\text{O})-$,
 25 b) $-\text{NH}-\text{SO}_2-$,
 c) $-\text{NH}-\text{C}(\text{O})-\text{NH}-$, or
 d) $-\text{SO}_2-\text{NH}-$;

wherein X_3 is

- a) C_1-C_6 alkyl, or
 30 b) $-(\text{CH}_2)_p-\text{R}_{15}$;

wherein X_4 is

- a) $-\text{NH}-\text{C}(\text{O})-$, or
 b) $-\text{NH}-\text{SO}_2-$;

wherein R_{10} is hydrogen;35 wherein R_{11} is

- a) hydrogen,

-32-

- b) C_1-C_6 alkyl,
- c) $-(CH_2)_n$ -aryl,
- d) $-(CH_2)_n-C_3-C_7$ cycloalkyl, or
- e) $-(CH_2)_n$ -het;

5 or wherein R_{10} and R_{11} taken together form a double bond;

or wherein R_3 and R_{11} taken together form

- a) C_3-C_8 cycloalkyl substituted by zero (0) to three (3) hydroxy, =N-OH, =O (oxo), or protected form thereof, or substituted at the α -position by R_{14} ; or
- b) a 5- or 6-membered saturated ring containing one (1) or two (2) oxygen

10 atoms;

wherein R_{12} is

- a) phenyl substituted by zero (0) to three (3) R_{13} , or
- b) naphthyl substituted by zero (0) to three (3) R_{13} ;

wherein R_{13} is

- 15 a) C_1-C_{10} alkyl substituted by zero (0) to three (3) halo,
- b) hydroxy,
- c) hydroxy- C_1-C_5 alkyl,
- d) $-(CH_2)_n-O-C_1-C_5$ alkyl substituted by zero (0) to three (3) hydroxy or halo,
- 20 e) $-(CH_2)_n-O-C_2-C_7$ alkenyl substituted by zero (0) to three (3) hydroxy or halo,
- f) halo,
- g) amino,
- h) amino C_1-C_5 alkyl,
- 25 i) mono-or di- C_1-C_5 alkylamino,
- j) $-C(O)-C_1-C_5$ alkyl,
- k) $-CHO$,
- l) $-COOH$,
- m) $-CON(R_7)_2$,
- 30 n) $-NHCOC_1-C_3$ alkyl,
- o) $-NHOH$,
- p) nitro,
- q) $-CN$,
- r) $-(CH_2)_n$ -phenyl,
- 35 s) $-COOC_1-C_5$ alkyl, or
- t) $-SO_2$ -phenyl substituted by zero (0) to three (3) C_1-C_5 alkyl,

-33-

- u) $-(CH_2)_n-X_4$ -phenyl, or
 v) $-(CH_2)_n-N=N$ -phenyl substituted by zero (0) or one (1) $-N(C_1-C_3$

alkyl)₂;wherein R_{14} is

- 5 a) $-(CH_2)_n$ -aryl,
 b) $-C_1-C_6$ alkyl, or
 c) $-(CH_2)_n-C_4-C_7$ cycloalkyl;

wherein R_{15} is a 5- or 6-membered saturated or unsaturated ring containing from one (1) to four (4) heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur;
 10 and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring, C_3-C_8 cycloalkyl, or another heterocycle; and substituted by zero (0) to three (3) R_{13} ;

wherein AA is an amino acid residue;

wherein P_1 is hydrogen or a nitrogen protecting group;

15 wherein m and n are independently zero (0) to five (5) inclusive;

wherein p is one (1) to five (5) inclusive;

wherein q is one (1) to five (5) inclusive; and

pharmaceutically acceptable salts thereof.

The present invention particularly provides such method wherein the size of the prostate
 20 in a male mammal is reduced or maintained.

For example, the present invention provides such method for compound of the formula

I

wherein R_1 is $-(CH_2)_n-CH(R_5)-(CH_2)_m-R_4$;wherein R_2 is hydrogen;

25 wherein R_3 is

- a) $R_4-(CH_2)_m-CH(R_6)-(CH_2)_n-$, or
 b) $R_4-(CH_2)_p-$;

wherein R_4 is

- 30 a) phenyl, or
 b) tetrahydropyranyl;

wherein R_5 is

- a) propyl, or
 b) cyclopropyl;

wherein R_6 is ethyl;

35 wherein m is zero (0) or one (1);

wherein n is zero (0);

wherein p is two (2);

wherein R₁₀ and R₁₁ taken together form a double bond.

The present invention also provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of the compound of formula I.

5 Finally, the present invention provides a process for making a compound of the formula CC-5 which comprises:

a) reacting a compound of the formula CC-3 with a compound of the formula CC-2 in a hydrocarbon solvent in the presence of a trialkylamine at an elevated temperature to yield a compound of the formula CC-4,

10 b) treating the compound of formula CC-4 with a base in a water/alcohol mixture,

c) treating the mixture of step b) with an acid to yield the compound of formula CC-5. (Refer to Chart CC below.)

The compounds of the present invention are named according to the IUPAC or CAS nomenclature system.

15 The carbon atoms content of various hydrocarbon-containing moieties is indicated by a prefix designating the minimum and maximum number of carbon atoms in the moiety, i.e., the prefix C_i-C_j indicates a moiety of the integer "i" to the integer "j" carbon atoms, inclusive. Thus, for example, C₁-C₃ alkyl refers to alkyl of one to three carbon atoms, inclusive, or ethyl, ethyl, propyl, and isopropyl.

20 Examples of alkyl of one to nine carbon atoms, inclusive, are methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, and nonyl, and all isomeric forms thereof, straight and branched.

Examples of alkenyl of one to five carbon atoms, inclusive, are ethenyl, propenyl, butenyl, pentenyl, and all isomeric forms thereof.

25 Examples of "halo" or "halogen" are fluoro, chloro and bromo.

By "amino acid residue" is meant the residue of a naturally occurring amino acid, such as: Alanine, Arginine, Asparagine, Aspartic acid, Cysteine, Glutamine, Glutamic Acid, Glycine, Histidine, Isoleucine, Leucine, Lysine, Methionine, Phenylalanine, Proline, Serine, Threonine, Tryptophan, Tyrosine, Valine, Aspartic acid or Asparagine, Glutamic acid or Glutamine; and
30 synthetic derivatives thereof. These amino acid residues may be in the L- or D- configuration and are readily known and available to those skilled in the art. These amino acid residues (or their N-terminal protected forms) are connected to a free amino group via their C-terminus.

The compounds of formula I of the present invention inhibit retroviral proteinases and thus inhibit the replication of the virus. They are useful for treating patients infected with
35 human immunodeficiency virus (HIV) which results in acquired immunodeficiency syndrome (AIDS) and related diseases.

More particularly, the compounds of the present invention are useful as novel human retroviral protease inhibitors. Therefore, the compounds inhibit retroviral proteases and thus inhibit the replication of the virus. They are useful for treating human patients infected with a human retrovirus, such as human immunodeficiency virus (strains of HIV-1 or HIV-2) or human T-cell leukemia viruses (HTLV-I or HTLV-II) which results in acquired immunodeficiency syndrome (AIDS) and/or related diseases.

The capsid and replicative enzymes (i.e. protease, reverse transcriptase, integrase) of retroviruses are translated from the viral gag and pol genes as polyproteins that are further processed by the viral protease (PR) to the mature proteins found in the viral capsid and necessary for viral functions and replication. If the PR is absent or nonfunctional, the virus cannot replicate. The retroviral PR, such as HIV-1 PR, has been found to be an aspartic protease with active site characteristics similar to those exhibited by the more complex aspartic protease, renin.

The term human retrovirus (HRV) includes human immunodeficiency virus type I, human immunodeficiency virus type II, or strains thereof, as well as human T cell leukemia virus 1 and 2 (HTLV-1 and HTLV-2) or strains apparent to one skilled in the art, which belong to the same or related viral families and which create similar physiological effects in humans as various human retroviruses.

Patients to be treated would be those individuals: 1) infected with one or more strains of a human retrovirus as determined by the presence of either measurable viral antibody or antigen in the serum and 2) in the case of HIV, having either an asymptomatic HIV infection or a symptomatic AIDS defining infection such as i) disseminated histoplasmosis, ii) isosporiasis (Isosporiasis, which is caused by *Isospora belli*, a coccidian parasite, is a diarrheal illness that occurs in AIDS patients when their CD4 counts get low. There are few if any effective drugs against *Isospora* or *Cryptosporidia*, a more common parasite that causes a similar chronic diarrhea and wasting in AIDS patients.), iii) bronchial and pulmonary candidiasis including pneumocystic pneumonia iv) non-Hodgkin's lymphoma or v) Kaposi's sarcoma and being less than sixty years old; or having an absolute CD4+ lymphocyte count of less than $500/\text{mm}^3$ in the peripheral blood. Treatment of these patients would consist of maintaining an inhibitory level of the compound used according to this invention in the patient at all times and would continue until the occurrence of a second symptomatic AIDS defining infection indicates alternate therapy is needed.

More specifically, an example of one such human retrovirus is the human immunodeficiency virus (HIV, also known as HTLV-III or LAV) which has been recognized as the causative agent in human acquired immunodeficiency syndrome (AIDS), although a minority opinion to the contrary has been expressed, P. Duesberg, Proc. Natl. Acad. Sci. USA, 86:755

- (1989). HIV contains a retro viral encoded protease, HIV-I protease, that cleaves the fusion polypeptides into the functional proteins of the mature viral particle, E.P. Lillehoj, et al., J. Virology, 62:3053 (1988); C. Debuck, et al., Proc. Natl. Acad. Sci., 84:8903 (1987). This enzyme, HIV-I protease, has been classified as an aspartyl protease and has a demonstrated
- 5 homology to other aspartyl proteases such as renin, L.H. Pearl, *et al.*, Nature 329:351 (1987); I. Katoh, *et al.*, Nature 329:654 (1987). Inhibition of HIV-I protease blocks the replication of HIV and thus is useful in the treatment of human AIDS, E.D. Clerq, J. Med. Chem. 29:1561 (1986). Inhibitors of HIV-I protease are useful in the treatment of HIV-infected individuals who are asymptomatic or symptomatic of AIDS.
- 10 Pepstatin A, a general inhibitor of aspartyl proteases, has been disclosed as an inhibitor of HIV-I protease, S. Seelmeier, *et al.*, Proc. Natl. Acad. Sci. USA, 85:6612 (1986). Other substrate derived inhibitors containing reduced bond isosteres or statine at the scissile position have also been disclosed, M.L. Moore, *et al.*, Biochem. Biophys. Res. Commun. 159:420 (1989); S. Billich, *et al.*, J. Biol. Chem. 263:17905 (1988); Sandoz, D.E. 3812-576-A.

- 15 Thus, the compounds of the present invention are useful for treating diseases caused by retroviruses, such as human acquired immunodeficiency disease syndrome (AIDS).

- The compounds are also useful for treating non-human animals infected with a retrovirus, such as cats infected with feline leukemia virus. Other viruses that infect cats include, for example, feline infectious peritonitis virus, calicivirus, rabies virus, feline
- 20 immunodeficiency virus, feline parvovirus (panleukopenia virus), and feline chlamydia. Exact dosages, forms and modes of administration of the peptides of the present invention to non-human animals would be apparent to one of ordinary skill in the art, such as a veterinarian.

- The compounds of formula I of the present invention are prepared as described in the Preparations and Examples below, or are prepared by methods analogous thereto, which are
- 25 readily known and available to one of ordinary skill in the art of organic synthesis.

CHART A

- The preparation of 6-aryl-4-hydroxy-2-pyrone (such as A-4: X is CH) and 3-alkylated-6-aryl-4-hydroxy-2-pyrone (such as A-5: X is CH, R is ethyl) are shown in Chart A.
- Deprotonation of ethyl acetoacetate of formula A-1, which is commercially available, with
- 30 potassium hydride and n-butyl lithium in tetrahydrofuran, followed by addition of ethyl benzoate, which is the compound of formula A-2 (wherein X is CH) affords ethyl 5-phenyl-3,5-dioxopentanoate of formula A-3 (wherein X is CH). Heating the compound of formula A-3 at 120 °C under reduced pressure (1 mm Hg, neat) affords 4-hydroxy-6-phenyl-2-pyrone, the compound of formula A-4 (wherein X is CH). Alkylation of the compound of formula A-4 by
- 35 heating with a number of the corresponding substituted benzyl bromides or treatment of the compound of formula A-4 with the corresponding substituted benzyl alcohols in the presence of

boron trifluoride-diethyl ether results in the desired product of formula A-5 (wherein X is CH and R is ethyl), which is the compound: 3-(.alpha.-ethylbenzyl)-4-hydroxy-6-phenyl-2H-pyran-2-one.

CHART B

5 The preparation of the compound of formula B-5 (wherein n is 1) which is the compound: 6-benzyl-3-(.alpha.-ethylbenzyl)-4-hydroxy-2H-pyran-2-one, and the compound of formula B-5 (wherein n is 2), which is the compound: 3-(.alpha.-ethylbenzyl)-6-phenethyl-4-hydroxy-2H-pyran-2-one, are shown in Chart B. The dianion of formula B-1 is generated by the same conditions as described in Chart A. Either ethyl phenylacetate of formula B-2 (wherein n is 1) or ethyl dihydrocinnamate of formula B-2 (wherein n is 2) is then added to give ethyl 6-phenyl-3,5-dioxohexanoate of formula B-3 (wherein n is 1) or ethyl 7-phenyl-3,5-dioxoheptanoate of formula B-3 (wherein n is 2), respectively. Formation of the pyrone ring in the compound of formula B-4 (wherein n is 1 or 2) is accomplished by heating the compound of formula B-3 (wherein n is 1 or 2, respectively) under reduced pressure. Heating of the compound of formula B-4 (wherein n is 1 or 2) with (±)-1-bromo-1-phenylpropane or treatment with (±)-1-phenylpropanol in the presence of boron trifluoride in dioxane gives the desired products of formula B-5 (wherein n is 1 or 2, respectively).

CHART C

20 The desired product of formula C-4, which is the compound: 4-hydroxy-6-phenethyl-3-(.alpha.-propyl-p-bromobenzyl)-2H-pyran-2-one, is obtained by heating the pyrone of formula C-3 (prepared in Chart B as the compound of formula B-4 (wherein n is 2)) with the compound of formula C-2 (wherein R is bromide). The requisite compound of formula C-2 (wherein R is bromide) is obtained by a two-step sequence starting from 4-bromobenzaldehyde, the compound of formula C-1. Treatment of the compound of formula C-1 with propylmagnesium bromide affords 1-(4'-bromophenyl)-1-butanol, the compound of formula C-2 (wherein R is OH). The resulting alcohol, the compound of formula C-2 (wherein R is OH), is then treated with 48% hydrobromic acid to give the desired bromide of formula C-2 (wherein R is bromide).

CHART D

30 O-allylation of 4-hydroxy-6-methyl-2-pyrone, the compound of formula D-1, with cinnamyl bromide is achieved to yield the compound of formula D-2. Claisen rearrangement of the resulting pyrone of formula D-2 is carried out in refluxing toluene to give the vinyl analogue of the formula D-3. Claisen product of formula D-3 is subjected to catalytic hydrogenation to afford the compound of formula D-4. Treatment of the compound of formula D-4 with two equivalents of lithium diisopropylamide in tetrahydrofuran followed by the addition of electrophile, such as benzyl bromide, gives the product of formula D-5, which is the compound: 3-(.alpha.-ethylbenzyl)-6-phenethyl-4-hydroxy-2H-pyran-2-one. This is the preferred process for

preparing this compound.

CHART E

A variety of analogues may be prepared by employing similar conditions which are used in the preparation of the compound of formula D-5 of Chart D. Under these conditions, 4-bromobenzyl bromide, 2-fluorobenzyl bromide, or allyl bromide are reacted with the dianion of formula E-1 (prepared in Chart D as the compound of formula D-4) rapidly to yield the compound of formula E-2 (wherein R is 4-bromobenzyl, 2-fluorobenzyl or 3-propylene), which are the compounds: 6-(p-bromophenethyl)-3-(.alpha.-ethylbenzyl)-4-hydroxy-2H-pyran-2-one; 3-(.alpha.-ethylbenzyl)-6-(o-fluorophenethyl)-4-hydroxy-2H-pyran-2-one; and 3-(.alpha.-ethylbenzyl)-4-hydroxy-6-(3-butenyl)-2H-pyran-2-one, respectively. However, reacting iodoethane and phenylethyl bromide with the compound of formula E-1 would require stirring the reaction mixture at room temperature for a few hours to yield the compound of formula E-2 (wherein R is ethyl or phenylethyl), which are the compounds: 3-(.alpha.-ethylbenzyl)-4-hydroxy-6-propyl-2H-pyran-2-one and 3-(.alpha.-ethylbenzyl)-4-hydroxy-6-(3-phenylpropyl)-2H-pyran-2-one, respectively.

CHART F

Treatment of the compound of formula F-1 (prepared as the compound of formula D-4 in Chart D) with 2 eq. of lithium diisopropylamide and tetrahydrofuran at -40°C, followed by the addition of phenyl isocyanate yields the compound of formula F-2, which is the compound: 3-(.alpha.-ethylbenzyl)-4-hydroxy-6-[[[(phenylamino)carbonyl]methyl]-2H-pyran-2-one.

CHART G

The preparation of the compound of formula G-2, which is the compound: 4-hydroxy-6-phenethyl-3-(.alpha.-vinylbenzyl)-2H-pyran-2-one, is achieved by the direct alkylation of the compound of formula G-1 (prepared as the compound of formula D-3 in Chart D) with benzyl bromide.

CHART H

Commercially available 6-methyl-4-hydroxy-2H-pyran-2-one of formula H-1 is reacted with commercially available α -ethylbenzyl alcohol of formula H-2 with acid catalyst to give the compound of formula H-3.

Treatment of the compound of formula H-3 (may also be prepared as the compound of formula D-4 in Chart D) with three equivalents of lithium diisopropylamide in tetrahydrofuran, followed by the sequential addition of benzyl bromide and ethyl iodide gives the compound of formula H-4 (wherein R₁ is benzyl and R₂ is ethyl) which is the compound: 3-(.alpha.-ethylbenzyl)-6-(.alpha.-ethylphenethyl)-4-hydroxy-2H-pyran-2-one. Under similar conditions, the compound of formula H-4 (wherein R₁ is ethyl and R₂ is ethyl) which is the compound: 3-(.alpha.-ethylbenzyl)-1-ethylpropyl-4-hydroxy-2H-pyran-2-one, is obtained by employing two

equivalents of ethyl iodide as electrophile.

CHART I

Alkylation of the anion of methylacetoacetate of formula I-1, which is commercially available, after treatment with sodium hydride, with α -ethylbenzyl bromide of formula I-2, which is commercially available, gives methyl 2-(α -ethylbenzyl)-acetoacetate of formula I-3. The corresponding dianion, which is generated from sequential treatment with sodium hydride and *n*-butyllithium, adds to propiophenone of formula I-4, which is commercially available, to give methyl 2-(α -ethylbenzyl)-5-hydroxy-3-oxo-5-phenyl-heptanoate of formula I-5. The methyl ester is then hydrolyzed with sodium hydroxide, and upon acidification with hydrochloric acid, the desired material, 6-ethyl-3-(α -ethylbenzyl)-6-phenyl-tetrahydropyran-2,4-dione of formula I-6 is isolated.

CHART J

Alkylation of the anion of methylacetoacetate of formula J-1 (also used in Chart I as the compound of formula I-1), which is commercially available, after treatment with sodium hydride, with 1-bromo-3-phenylpropane formula J-2, which is commercially available, gives ethyl 2-(3-phenylpropyl)-acetoacetate of formula J-3. The corresponding dianion, which is generated from sequential treatment with sodium hydride and *n*-butyllithium, adds to 3-pentanone of formula J-4, which is commercially available, to give methyl 2-(3-phenylpropyl)-5-phenyl-5-hydroxy-3-oxo-heptanoate of formula J-5. The methyl ester is then hydrolyzed with sodium hydroxide, and upon acidification with hydrochloric acid, the desired material, 6-ethyl-3-(3-phenylpropyl)-tetrahydropyran-2,4-dione of formula J-6, is isolated.

CHART K

Chart K offers an alternative highly effective way to introduce C-3 substituents on the 4-hydroxy- α -pyrone and 5,6-dihydro-4-hydroxy-2H-pyran-2-one nucleus. Allylic carbonates of formula K-2 (a, b and c) and nucleophile 5,6-dihydro-4-hydroxy-2-pyrones of formula K-1 (a, b and c) are treated with palladium acetate and triphenylphosphine in toluene at 50 °C to yield compounds of formula K-3 (a, b and c). Representative examples of this reaction follow in Chart K. Also, it is possible to employ allylic carbonates containing substitution in the phenyl ring (Chart K, eq. a,b). In cases where diastereomeric products are possible (Chart K, eq. a,b), chromatographically inseparable mixtures are formed. The final products are obtained via acylation and reduction. In some cases, it is possible to isolate one diastereomer of the product via successive recrystallation. The mother liquors contain a mixture enriched in the other diastereomer, but attempts to purify them via further recrystallizations may fail. Subsequent chemical manipulations on the substituents at the 6-position of the 5,6-dihydropyran-2-one ring are performed by those skilled in the art.

CHART L

Chart L describes a generic procedure for the synthesis of C-3 α -branched substituted 4-hydroxy-2-pyrones or 4-hydroxy-5,6-dihydropyran-2-ones. The key reaction involves a palladium catalyzed allylic alkylation of the cyclic β -ketoester nucleophile of formula L-1 (wherein R_{11} and R_3 are defined above) utilizing a silyl substituted allylic carbonate of formula L-2. Subsequent desilylation and reduction of the compound of formula L-3 (wherein R_{11} and R_3 are defined above) affords the desired final products, such as compounds of the formula L-4 (wherein R_{11} is phenyl and R_3 is propyl or cyclohexyl; and R_8 is hydrogen or hydroxy) which are the compounds: 4-hydroxy-6-propyl-6-phenyl-3-(1-phenylpropyl)-2H-pyran-2-one; 4-hydroxy-6-phenyl-6-propyl-3-[1-(2-hydroxyphenyl)-propyl]-2H-pyran-2-one; and 4-hydroxy-6-cyclohexyl-6-phenyl-3-[1-(3-hydroxyphenyl)propyl]-2H-pyran-2-one. This method is especially useful to synthesize 6,6-disubstituted-5,6-dihydro-2H-pyran-2-ones, such as those in Charts K and L.

CHART M

The dianion of commercially available 4-hydroxy-6-methyl-2-pyrone of formula M-1 is generated by deprotonation with two equivalents of lithium diisopropylamide in tetrahydrofuran and hexamethylphosphoramide. Alkylation with benzyl bromide gives the compound of formula M-2. It is then treated with two equivalents of lithium diisopropylamide in tetrahydrofuran and hexamethylphosphoramide, followed by ethyl iodide to give the compound of formula M-3. Reaction between the compound of formula M-3 and the compound of formula O-5, prepared as described in Chart O, in benzene with *p*-toluenesulfonic acid catalyst in the presence of molecular sieves affords the compound of formula M-4, which is 3-(α -Cyclopropyl-*meta*-(*tert*-butyloxycarbonylamino)benzyl)-6-(α -ethyl-phenethyl)-4-hydroxy-2H-pyran-2-one.

Hydrogenolysis of the compound of formula M-4 in methanol with hydrogen and palladium on charcoal gives the free amine of formula M-5. Condensation of the compound of formula M-5 with *tert*-butyloxycarbonyl- β -alanine in dichloromethane using diisopropylcarbodiimide gives the compound of formula M-6, which is N-(3-Cyclopropyl-[6-(1-ethyl-phenethyl)-4-hydroxy-2-oxo-5,6-dihydro-2H-pyran-3-yl]-methyl)-phenyl)-3-(*tert*-butyloxycarbonylamino)-propionamide. The amine M-5 is reacted with alkyl sulfonyl chloride or aryl sulfonyl chloride in the presence of pyridine to give compound of formula M-7 wherein R_1 is aryl, e.g., phenyl, 3-(α -Cyclopropyl-*meta*-(phenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one.

CHART N

Treatment of commercially available 4-hydroxy-6-methyl-2-pyrone of formula N-1 with three equivalents of lithium diisopropylamide in tetrahydrofuran and hexamethylphosphoramide is followed by bromomethylcyclopropane to afford the compound of formula N-2. Reaction between the compound of formula N-2 and the compound of formula O-5, prepared as described

-41-

in benzene with *p*-toluenesulfonic acid catalyst in the presence of molecular sieves gives the compound of formula N-3, which is 3-(α -Cyclopropyl-*meta*-(*tert*-carbonylamino)benzyl)-6-(α -cyclopropylmethyl-cyclopropylethyl)-4-hydroxy-2H-pyran-

hydrogenolysis of the compound of formula N-3 in methanol with hydrogen and Raney nickel on charcoal gives the free amine of formula N-4. Condensation of the compound of formula N-4 with 3-(1-indolyl)-propionic acid in dichloromethane and dimethylformamide using carbodiimide gives the compound of formula N-5, which is N-(3-{Cyclopropyl-[6-(2-cyclopropyl-1-cyclopropylmethyl-ethyl)-4-hydroxy-2-oxo-5,6-dihydro-2H-pyran-3-yl]-methyl}-1-indol-1-yl)-propionamide.

CHART O

Reaction of commercially available cyclopropyl phenyl ketone of formula O-1 with *p*-toluenesulfonic acid affords the compound of formula O-2. Reduction of the compound of formula O-2 in methanol with hydrogen catalyzed by platinum on carbon gives the amine of formula O-3. The compound of formula O-3 is treated with benzylchloroformate and triethylamine in dichloromethane to give the compound of formula O-4. Reduction of the compound of formula O-4 with sodium borohydride in tetrahydrofuran and ethanol gives the compound of formula O-5.

CHART P

Reaction between 5-bromo-4-hydroxy-6-methyl-pyran-2-one of formula P-1 (preparation of which is described in *Syn. Comm.* 1984, 14, 521) and commercially available 1-phenyl-2-propanone in benzene catalyzed by *p*-toluenesulfonic acid gives the compound of formula P-2. Reaction of the compound of formula P-2 with lithium diisopropyl amide and commercially available bromomethylcyclopropane affords the compound of formula P-3, which is 5-Bromomethyl-cyclopropylmethyl-ethyl)-4-hydroxy-3-(1-phenyl-propyl)-pyran-2-one.

CHART Q

Reaction of 3-(cyclopropyl-phenyl-methyl)-4-hydroxy-6-methyl-pyran-2-one of formula Q-1 with lithium diisopropylamide, followed by 2-(2-methoxy-ethoxy)-ethyl bromide gives the compound of formula Q-2. Treatment of the compound of formula Q-2 with lithium diisopropylamide, followed by ethyl iodide, gives the compound of formula Q-3, which is 3-(cyclopropyl-phenyl-methyl)-4-hydroxy-5-(2-(2-methoxy-ethoxy)-ethyl)-6-propyl-pyran-2-one.

CHART R

Reaction of commercially available 1,3-diphenylacetone of formula R-1 with the anion of 2,2,4,4-tetramethylphosphonoacetate gives the compound of formula R-2, which is 1,3-diphenyl-2-(2,2,4,4-tetramethylphosphono)propan-1-one. Hydrogenolysis of the compound of formula R-2 in ethyl acetate with 50 psi of hydrogen and platinum on carbon to give the compound of formula R-3.

compound of formula R-3. Treatment of the compound of formula R-3 with lithium diisopropylamide, followed by diketene, affords the compound of formula R-4, which is treated with trifluoroacetic acid and followed by acetic anhydride to give the compound of formula R-5. Treatment of the compound of formula R-5 with lithium diisopropylamide, followed by (bromomethyl)cyclopropane, gives the compound of formula R-6, which is 3-(1-Benzyl-2-phenyl-ethyl)-6-(2-cyclopropyl-1-cyclopropylmethyl-ethyl)-4-hydroxy-pyran-2-one.

CHART S

The compound of formula S-1 is prepared by the method of Y.S. Shabarov, N.A. Donskaya and R.Y. Lovina, Zh. Obshch. Khim., 33:3434 (1963) (CA60:1624c). The compound of formula S-3 is prepared from compounds S-1 and S-2 (M-2) by the procedure described in Example 1 below. The final compound of formula S-4, which is 4-Hydroxy-3-(1-phenylcyclobutyl)-6-[1-(phenylmethyl)propyl]-2H-pyran-2-one, is prepared by an analogous procedure to Example 6.

CHART T

The compound of formula T-5, which is 4-Hydroxy-3-(1-phenyl-2-propenyl)-1-oxaspiro[5.7]tridec-3-en-2-one, is prepared from cyclooctanone (compound T-1) by procedures described in Preparations 16A, 16B and 16C below. The compound of formula T-6, which is 4-Hydroxy-3-(1-phenylpropyl)-1-oxaspiro[5.7]tridec-3-en-2-one, is prepared from compound T-5 by procedure described in Preparation 16D below.

CHART U

The unsaturated amide U-1 (Chemistry Letters (1981, 913-16) is treated with ethyl magnesium bromide in diethyl ether at -40°C to yield U-2. Acid hydrolysis of U-2 affords the intermediate U-3. In a manner similar to the above, treatment of U-4 with phenyl magnesium bromide in diethyl ether affords U-5 which upon treatment with acid affords intermediate U-6. Compounds of the formula U-3 and U-6 wherein phenyl is substituted with, e.g., halogen, trifluoromethyl, -NHBOC, -NHCBZ, NHSO₂Ph, or N-(1,1,4,4-tetramethyl-1,4-bisdisilethylene) (e.g., see Formula BBB-5 in Chart BBB), or wherein phenyl is replaced with optionally substituted heterocycles, e.g., furan and thiophene, are prepared following the above procedure.

CHART V

The unsaturated amide V-1 (Hruby, et. al., J. Org. Chem. (1993) 58, 766) is treated with phenyl magnesium bromide in the presence of a copper catalyst in tetrahydrofuran to yield V-2. Hydrolysis of V-2 yields V-3 (same as U-6). In a similar fashion, V-4 is converted to V-5 and finally to V-6 (same as U-3). Compounds of the formula V-3 and V-6 wherein phenyl is substituted with, e.g., halogen, trifluoromethyl, -NHBOC or -NHCBZ, or wherein phenyl is replaced with optionally substituted heterocycles, e.g., furan and thiophene, are prepared

following the above procedure. Also beginning with compounds of the formula V-7 and V-8, compounds of the formula V-3 and V-6 wherein the ethyl group is replaced with a cyclopropyl are prepared by the procedure of this chart.

CHART W

- 5 [4S,5R]-(+)-4-methyl-5-phenyl-2-oxazolidinone, which is commercially available, is dissolved in THF and cooled to -78°C . n-Butyl lithium is added over 5 minutes and stirring continued for one hour. Butyryl chloride is added in a single portion to yield W-1 after aqueous work up. W-1 is treated with lithium diisopropyl amide (LDA) and reacted with W-2, which is commercially available, (or with other benzyl halides substituted with, e.g., halogen, alkoxy, -
- 10 CN, nitro or trifluoromethyl, to achieve the substituted compounds corresponding to the following) to yield W-3 as a single diastereomer. Treatment of W-3 with lithium hydroxide and hydrogen peroxide in a THF/water mixture affords W-4 [R] which is then reacted with methyl lithium in ethyl ether to yield methyl ketone W-5. Carboxylation of W-5 yields the β -ketoacid W-6 (see Hogeveen, Menge Tetrahedron Letters (1986) 2767) which is treated with acetic
- 15 anhydride and acid in the presence of acetone to afford the 1,3-dioxin-4-one derivative W-7.
- W-4 is also treated with oxalyl chloride to yield W-8. W-8 is reacted with the lithium enolate derived from t-butylacetate (W-9; enolate formed in THF with lithium diisopropylamide at -78°C), to yield the β -ketoester W-10. Treatment of W-10 with H_2SO_4 /Acetic anhydride/acetone then yields W-7.(Kaneko, Sato, Sakaki, Abe J. Heterocyclic Chem. (1990)
- 20 27:25).

CHART X

- [4R,5S]-(-)-4-methyl-5-phenyl-2-oxazolidinone, which is commercially available, is dissolved in THF and cooled to -78°C . n-Butyl lithium is added over 5 minutes and stirring continued for one hour. Butyryl chloride is added in a single portion to yield X-1 after aqueous
- 25 work up. X-1 is treated with lithium diisopropyl amide (LDA) and reacted with X-2, which is commercially available, (or with other benzyl halides substituted with, e.g., halogen, alkoxy, - CN, nitro or trifluoromethyl, to achieve the substituted compounds corresponding to the following) to yield X-3 as a single diastereomer. Treatment of X-3 with lithium hydroxide and hydrogen peroxide in a THF/water mixture affords X-4 [S] which is then reacted with methyl
- 30 lithium in ethyl ether to yield methyl ketone X-5. Carboxylation of X-5 yields the β -ketoacid X-6 (see Hogeveen, Menge Tetrahedron Letters (1986) 2767) which is treated with acetic anhydride and acid in the presence of acetone to afford the 1,3-dioxin-4-one derivative X-7.
- X-4 is also treated with oxalyl chloride to yield X-8. X-8 is reacted with the lithium enolate of tert-butylacetate (X-9) as in the above example to yield X-10. Treatment of X-10
- 35 with H_2SO_4 /Acetic anhydride/acetone then yields X-7.(Kaneko, Sato, Sakaki, Abe J. Heterocyclic Chem. (1990) 27:25).

-44-

CHART Y

Treatment of Y-1, which is commercially available, with oxalyl chloride in methylene chloride affords the acid chloride Y-2. Treatment of a mixture of Y-2 and 2,2,6-trimethyl-4H-1,3-dioxin-4-one (Y-3), which is commercially available, with triethyl amine (TEA) in toluene at an elevated temperature affords the pyrone Y-4. Treatment of Y-4 with Na_2CO_3 in methanol affords the hydroxy pyrone Y-5 (3- α -methylbenzyl-4-hydroxy-6-methyl-2H-pyran-2-one) and the ester Y-6.

CHART Z

Treatment of Z-1 (which is the same as U-3) with oxalyl chloride in methylene chloride affords the acid chloride Z-2. Treatment of a mixture of Z-2 and commercially available 2,2,6-trimethyl-4H-1,3-dioxin-4-one (Z-3) (which is the same as Y-3) with triethyl amine (TEA) in toluene at an elevated temperature affords the pyrone Z-4. Treatment of Z-4 with Na_2CO_3 in methanol affords the hydroxy pyrone Z-5 (3[R]- α -ethylbenzyl-4-hydroxy-6-methyl-2H-pyran-2-one) and the ester Z-6.

CHART AA

Treatment of AA-1 (which is the same as U-3) with oxalyl chloride in methylene chloride affords the acid chloride AA-2. Treatment of a mixture of (S)-3-phenylvaleryl chloride (AA-2) (which is the same as Z-2) and (R)-2,2-dimethyl-6-(α -ethylphenethyl)-4H-1,3-dioxin-4-one (AA-3) (which is the same as W-7) with triethyl amine (TEA) in toluene at elevated temperatures affords the pyrone AA-4. Basic hydrolysis of AA-4 in methanol affords the final hydroxy pyrone AA-5 (3-([R]- α -ethylbenzyl)-4-hydroxy-6-([R]- α -ethylphenethyl)-2H-pyran-2-one) and the ester AA-6 (which is the same as Z-6).

CHART BB

Treatment of BB-1 (which is the same as U-3) with oxalyl chloride in methylene chloride affords the acid chloride BB-2. Treatment of a mixture of (S)-3-phenylvaleryl chloride (BB-2) (which is the same as Z-2) and (S)-2,2-dimethyl-6-(α -ethylphenethyl)-4H-1,3-dioxin-4-one (BB-3) (which is the same as X-7) with triethyl amine (TEA) in toluene at elevated temperatures affords the pyrone BB-4. Basic hydrolysis of BB-4 in methanol affords the final hydroxy pyrone BB-5 (3-([R]- α -ethylbenzyl)-4-hydroxy-6-([S]- α -ethylphenethyl)-2H-pyran-2-one) and the ester BB-6 (which is the same as Z-6).

CHART CC

Treatment of CC-1 (which is the same as U-6) with oxalyl chloride in methylene chloride affords the acid chloride CC-2. Treatment of a mixture of (R)-3-phenylvaleryl chloride (CC-2) and (R)-2,2-dimethyl-6-(α -ethylphenethyl)-4H-1,3-dioxin-4-one (CC-3) (which is the same as W-7) with a trialkylamine, e.g., triethyl amine (TEA) in a hydrocarbon solvent, e.g., toluene, at elevated temperatures (e.g. 100°C) affords the pyrone CC-4. Basic hydrolysis of CC-

4, using, e.g., sodium carbonate, in a water/alcohol (e.g., methanol) mixture (about 1:9), followed by treatment with an acid; e.g., 1 N hydrochloric acid, affords the final hydroxy pyrone CC-5 (3-([S]- α -ethylbenzyl)-4-hydroxy-6-([R]- α -ethylphenethyl)-2H-pyran-2-one; and the ester CC-6.

- 5 Also removal of triethyl amine hydrochloride by filtration followed by addition of a molar equivalent of sodium hydroxide (methanol) to the toluene solution of CC-4 yields the sodium salt of CC-5 as a precipitate. Collection of that precipitate is conducted by standard procedures.

CHART DD

- 10 Treatment of DD-1 (which is the same as U-6) with oxalyl chloride in methylene chloride affords the acid chloride DD-2. Treatment of a mixture of (R)-3-phenylvaleryl chloride (DD-2) (which is the same as CC-2) and (S)-2,2-dimethyl-6-(α -ethylphenethyl)-4H-1,3-dioxin-4-one (DD-3) (which is the same as X-7) with triethyl amine (TEA) in toluene at elevated temperatures affords the pyrone DD-4. Basic hydrolysis of DD-4 in methanol affords the final
15 hydroxy pyrone DD-5 (3-([S]- α -ethylbenzyl)-4-hydroxy-6-([S]- α -ethylphenethyl)-2H-pyran-2-one) and the ester DD-6 (which is the same as CC-6).

 The synthesis of all four diastereomers of 3-(α -ethylbenzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one are preferably obtained by following the procedures of Charts AA, BB, CC and DD.

20

CHART EE

- (R)-3-Phenylvaleric acid (EE-1) (which is the same as U-3) is converted to the corresponding methyl ester with thionyl chloride in methanol to yield EE-2 (which is the same as Z-6). EE-2 is treated with a strong base such as lithium diisopropylamide followed by trimethylsilyl chloride to give EE-3. A mixture of EE-3 and EE-4 (W-7) is heated in an organic
25 solvent such as toluene followed by treating the reaction mixture with acid to yield the final product EE-5 (which is the same as AA-5) (3-([R]- α -ethylbenzyl)-4-hydroxy-6-([R]- α -ethylphenethyl)-2H-pyran-2-one).

CHART FF

- A mixture of FF-1 (which is the same as EE-3 and derived from (S)-3-phenylvaleric
30 acid (U-3), and FF-2 (which is the same as X-7 in Chart X) is heated in an organic solvent such as toluene followed by treating the reaction mixture with acid to yield FF-3 (which is the same as BB-5) (3-([R]- α -methylbenzyl)-4-hydroxy-6-([S]- α -ethylphenethyl)-2H-pyran-2-one).

CHART GG

- (R)-3-Phenylvaleric acid (GG-1) (which is the same as U-6) is converted to the
35 corresponding methyl ester with thionyl chloride in methanol to yield GG-2 (which is the same as CC-6). GG-2 is treated with a strong base such as lithium diisopropyl amide followed by

trimethylsilyl chloride to give GG-3. A mixture of GG-3 and GG-4 (W-7) is heated in an organic solvent such as toluene followed by treating the reaction mixture with acid to yield the final product (GG-5) (which is the same as CC-5) (3-([S]- α -methylbenzyl)-4-hydroxy-6-([R]- α -ethylphenethyl)-2H-pyran-2-one).

5

CHART HH

A mixture of HH-1 (which is the same as GG-3 in Chart GG) and HH-2 (X-7) is heated in an organic solvent such as toluene followed by treating the reaction mixture with acid to yield the final product HH-3 (which is the same as DD-5) (3-([S]- α -methylbenzyl)-4-hydroxy-6-([S]- α -ethylphenethyl)-2H-pyran-4-one).

10

CHART II

Furfuryl alcohol (II-1), which is commercially available, is treated with chloromethyl methyl ether in the presence of diisopropylethylamine in an organic solvent to yield the protected alcohol II-2. II-2 is treated with n-butyl lithium at low temperature in an ether solvent for several hours followed by the addition of cyclopropyl carboxaldehyde, which is
15 commercially available, to give alcohol II-3. A mixture of alcohol II-3 and pyrone II-4, which is commercially available, is treated with a catalytic amount of trifluoroacetic acid in methylene chloride to yield II-5. II-5 is treated with 2.2 equivalents of LDA followed by ethyl iodide to yield II-6. Treatment of II-6 with 2.2 equivalents of LDA followed by benzyl bromide yields the final product II-7, which is treated with mild acid to give the final product II-8 (3-(α -
20 cyclopropyl((5-hydroxymethyl)furfur-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-4-one). In the procedure above, other alkyl aldehydes are used in place of cyclopropyl carboxaldehyde to achieve alkyl compounds corresponding to II-3. Also, other alkyl or cycloalkyl halides are used in place of ethyl iodide to achieve compounds corresponding to II-6, and other benzyl halides substituted with, e.g., halogen, trifluoromethyl, -CN, nitro or alkoxy, are used in place of benzyl
25 bromide to achieve substituted compounds corresponding to II-7.

CHART JJ

Treatment of II-8 with methanesulphonyl chloride in the presence of a base such as pyridine gives the sulfonate JJ-1. Treatment of JJ-1 with sodium methoxide in methanol yields the final product JJ-2. Treatment of JJ-1 with sodium azide in an organic solvent affords the
30 final product, azide JJ-3, which is reduced with hydrogen (Pd/carbon) to give the final product JJ-4. JJ-4 is acylated with acetyl chloride in the presence of triethyl amine in a chlorocarbon or ether solvent, or in pyridine without additional base, to give the final product JJ-5 or reacted with an alkyl or arylsulphonyl halide to give the final product, sulphonate JJ-6. JJ-3 is reacted with methyl propionate in an organic solvent at elevated temperatures to yield the final product
35 JJ-7. Other alkyl alcohols are used in place of methanol, which is used in preparing JJ-2 from JJ-1, to give the corresponding alkyl analogs of JJ-2. Other acid chlorides are used in place of

-47-

acetyl chloride, which is used in preparing JJ-5 from JJ-4, to give the corresponding analogs of JJ-5. Other acetylenes, substituted with alkyl and aryl groups, are used in place of methyl propionate, which is used in preparing JJ-7 from JJ-3, to achieve the corresponding analogs of JJ-7. Aryl or heterocycle substituted sulphonyl halides are used in preparing the corresponding
5 analogs of JJ-6.

CHART KK

KK-1 (JJ-4) is reacted with 1,1-bis(methylthio)-2-nitroethylene (KK-2), which is commercially available, in an organic solvent to give the final product KK-3. Reaction of KK-3 with an equivalent of a primary or secondary amine gives the final product KK-4. In a similar
10 fashion, KK-1 (JJ-4) is reacted with dimethyl N-cyanothioiminocarbonate (KK-5), which is commercially available, to give the final product KK-6 which is reacted with a primary or secondary amine to give the final product KK-7. Other amines, such as primary and secondary amines, are used in place of isopropyl amine to prepare the corresponding analogs of KK-4 and KK-7.

CHART LL

LL-1, which is commercially available, is added to a saturated solution of NaHCO_3 . To that suspension is added benzyl chloroformate to yield LL-2. LL-2 is dissolved in methylene chloride and cooled to 0°C . Cyclopropyl carboxylic acid chloride, which is prepared from commercially available cyclopropane carboxylic acid using oxalyl chloride, is added followed by
20 an excess of AlCl_3 . The reaction is poured into ice water to yield LL-3. Reduction of LL-3 with sodium borohydride in a mixture of THF and ethanol gives LL-4. Treatment of a solution of LL-4 and pyrone LL-5 (which is the same as M-3) in methylene chloride with trifluoroacetic acid gives final product LL-6. Hydrogenation of LL-6 gives the final product LL-7 (3-(α -cyclopropyl((5-aminomethyl)furfur-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-
25 one)(which is the same as JJ-4). Other alkyl acid chlorides are used in place of cyclopropyl carboxylic acid chloride, which is used in preparing LL-3 from LL-2, to achieve the following corresponding analogs.

CHART MM

MM-1, which is commercially available, is added to a saturated solution of NaHCO_3 .
30 To that suspension is added benzyl chloroformate to yield MM-2. MM-2 is dissolved in methylene chloride and cooled to 0°C . Cyclopropyl carboxylic acid chloride, prepared from commercially available cyclopropane carboxylic acid using oxalyl chloride, is added followed by an excess of AlCl_3 . The reaction is poured into ice water to yield MM-3. Reduction of MM-3 with sodium borohydride in a mixture of THF and ethanol gives MM-4. Treatment of a
35 solution of MM-4 and pyrone MM-5 (which is the same as M-3) in methylene chloride with trifluoroacetic acid gives the final product MM-6. Hydrogenation of MM-6 gives the final

-48-

product MM-7 (3-(α -cyclopropyl((5-aminomethyl)thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one). Treatment of MM-7 with phenylsulphonylchloride gives the final product MM-8. Other alkyl acid chlorides and substituted heterocycles are used in place of cyclopropyl carboxylic acid to achieve analogs corresponding to M-3. Other substituted
5 arylsulfonyl halides are used in place of phenylsulfonyl chloride to achieve analogs corresponding to MM-8.

CHART NN

A mixture of NN-1, which is commercially available, and cyclopropylcarboxylic acid chloride, which is prepared from commercially available cyclopropane carboxylic acid, is treated
10 with a Lewis acid such as $AlCl_3$ in methylene chloride at $0^\circ C$ to yield NN-2. Treatment of NN-2 with sodium borohydride in an alcohol solvent gives NN-3. Treatment of a mixture of NN-3 and NN-4 (which is the same as M-3) in methylene chloride or toluene with an anhydrous acid such as trifluoroacetic acid or p-toluenesulfonic acid gives the final product NN-5. Treatment of NN-5 with azasulphene (NN-6), S. K. Gupta, Synthesis, p. 39 (1977), then affords
15 the final product NN-7. In a similar manner, treatment of NN-5 with chlorosulfonic acid followed by addition of aniline also yields NN-7 in a two-step protocol. Aniline substituted by one or more halogen, alkoxy, trifluoromethyl, alkyl, nitro and -CN, are also used in this process to yield substituted analogs of NN-7.

CHART OO

Thiophen-2-yl methanol (OO-1), which is commercially available, is treated with chloromethyl methyl ether in the presence of diisopropylethylamine in an organic solvent to yield the protected alcohol OO-2. OO-2 is treated with n-butyl lithium at low temperature in an ether solvent for several hours followed by the addition of cyclopropyl carboxaldehyde to give alcohols OO-3 and OO3a. A mixture of alcohol OO-3 and pyrone OO-4 (which is the same as
25 D-1) is treated with a catalytic amount of trifluoroacetic acid in methylene chloride to yield OO-5. OO-5 is treated with 2.2 equivalents of LDA followed by ethyl iodide to yield OO-6. Treatment of OO-6 with 2.2 equivalents of LDA followed by benzyl bromide yields the final product OO-7 which is treated with mild acid to give the final product OO-8 (3-(α -cyclopropyl((5-hydroxymethyl)thiophen-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-4-one).
30 In the procedure above, other alkyl aldehydes are used in place of cyclopropyl carboxaldehyde to achieve alkyl compounds corresponding to OO-3. Also, other alkyl or cycloalkyl halides are used in place of ethyl iodide to achieve compounds corresponding to OO-6, and other benzyl halides substituted with, e.g., halogen, trifluoromethyl, -CN, nitro or alkoxy, are used in place of benzyl bromide to achieve substituted compounds corresponding to OO-7.

35

CHART PP

Treatment of OO-8 with methanesulphonyl chloride in the presence of a base such as triethylamine gives the sulfonate PP-1. Treatment of PP-1 with sodium methoxide in methanol yields the final product PP-2. Treatment of PP-1 with sodium azide in an organic solvent affords the final product, azide PP-3, which is reduced with hydrogen (Pd/carbon) to give the final product PP-4. PP-4 is acylated with acetyl chloride in the presence of triethyl amine in a chlorocarbon or ether solvent, or in pyridine without additional base, to give the final product PP-5 or reacted with an alkyl or arylsulphonyl halide to give the final product, sulphonate PP-6 (N-(5-(1-cyclopropyl)-1-(4-hydroxy-6-(*a*-ethylphenethyl)-2H-pyron-4-one-3-yl)methyl)thiophen-2-yl phenyl sulphonamide). PP-3 is reacted with methyl propiolate in an organic solvent at elevated temperatures to yield the final product PP-7. Other alkyl alcohols are used in place of methanol, which is used in preparing PP-2 from PP-1, to give the corresponding alkyl analogs of PP-2. Other acid chlorides are used in place of acetyl chloride, which is used in preparing PP-5 from PP-4, to give the corresponding analogs of PP-5. Other acetylenes, substituted with alkyl and aryl groups, are used in place of methyl propionate, which is used in preparing PP-7 from PP-3, to achieve the corresponding analogs of PP-7. Aryl or heterocycle substituted sulphonyl halides are used in preparing the corresponding analogs of PP-6.

CHART QQ

A mixture of QQ-1 (OO-3a from Chart OO) and QQ-2 (which is the same as D-1) in methylene chloride is treated with a catalytic amount of trifluoroacetic acid which yields QQ-3. QQ-3 is treated with 3.3 equivalents of lithium diisopropylamide (LDA) in an ether solvent below room temperature followed by the addition of ethyl iodide to yield the final product QQ-4. Treatment of QQ-4 with 3.3 equivalents of LDA in an ether solvent followed by the addition of benzyl bromide yields the final product QQ-5 (which is the same as OO-8).

CHART RR

RR-1 (PP-4) is reacted with 1,1-bis(methylthio)-2-nitroethylene (RR-2), which is commercially available, in an organic solvent to give the final product RR-3. Reaction of RR-3 with an equivalent of a primary or secondary amine gives the final product RR-4. In a similar fashion, RR-1 is reacted with dimethyl N-cyanothioiminocarbonate (RR-5), which is commercially available, to give the final product RR-6 with is reacted with a primary or secondary amine to give the final product RR-7. Other amines, such as primary and secondary amines, are used in place of isopropyl amine to prepare the corresponding analogs of RR-4 and RR-7.

CHART SS

A mixture of SS-1, which is commercially available, and cyclopropylcarboxylic acid chloride, which is prepared from commercially available cyclopropane carboxylic acid, is treated with a Lewis acid such as AlCl_3 in methylene chloride at 0°C to yield SS-2. Treatment of SS-2

with sodium borohydride in an alcohol solvent gives SS-3. Treatment of a mixture of SS-3 and SS-4 (which is the same as M-3) in methylene chloride or toluene with an anhydrous acid, such as trifluoroacetic acid or p-toluenesulfonic acid, gives the final product SS-5. Treatment of SS-5 with azasulphene SS-6, S. K. Gupta, Synthesis, p. 39 (1977), then affords the final product SS-

- 5 7. In a similar manner, treatment of SS-5 with chlorosulfonic acid followed by addition of aniline also yields SS-7 in a two-step protocol. Aniline substituted by one or more halogen, alkoxy, trifluoromethyl, alkyl, nitro and -CN, is also used in this process to yield substituted analogs of SS-7.

CHART TT

- 10 Pyrone TT-1 (which is the same as Q-1) is treated with two equivalents of lithium diisopropylamide in an ether solvent. An aryl aldehyde is added at low temperature and the reaction quenched by adding a saturated solution of NH_4Cl . This affords the final product TT-2. Additionally, TT-1 is treated with 2.2 equivalents of lithium diisopropylamide (LDA) in an ether solvent followed by the addition of ethyl iodide to give TT-3. To that solution is added
15 another equivalent of LDA followed by benzaldehyde to yield the final product TT-4.

CHART UU

- Carboxylic acids UU-1 and UU-7 are prepared by methodology described in J. Amer. Chem. Soc. (1981) 103:2127, and Tetrahedron Letters (1986) 27:897. The β -hydroxyl group in both UU-1 and UU-7 is protected by reacting the hydroxy acid with t-butyldimethylsilyl
20 chloride in DMF in the presence of imidazole (or 2,6-lutidine, ethyldiisopropylamine) followed by treatment with aqueous base to yield the free carboxylic acid. The carboxylic acid is treated with oxalyl chloride (or alternate reagent) to yield acid chlorides UU-2 and UU-8. If required, another silyl derived protecting group such as the t-butyldiphenylsilyl group is used, or some other suitable alcohol protecting group. Both UU-2 and UU-8 are reacted with the lithium
25 enolate derived from tert-butylacetate (LDA/THF/-78C) to yield β -ketoesters UU-3 and UU-9. Treatment of UU-3 and UU-9 with H_2SO_4 /acetic anhydride/acetone yields UU-4 and UU-10 [Kaneko, Sato, Sakaki, Abe J. Heterocyclic Chem. (1990) 27:25], both of which react with acid chloride UU-5 in toluene in the presence of triethylamine to give the final products UU-6 and UU-11. Oxidation of UU-6 and UU-11 with CrO_3 or Swern conditions yield the final products
30 UU-12 and UU-14 both of which when treated with sodium borohydride (or other hydride reagents) give mixtures of diastereomers. Reduction of UU-12 yields UU-6 and UU-13 as a separable mixture of diastereomers. Reduction of UU-14 yields UU-11 and UU-15 as a separable mixture of diastereomers. The remaining diastereomeric products are prepared using this same strategy but using the (S) acid chloride UU-16 in place of UU-5.

35

CHART VV

Chart VV is a modified version of Chart L above. This chart describes the

-51-

palladium catalyzed allylic alkylation of the cyclic β -ketoester nucleophile of formula VV-1 (wherein, e.g., R_1 is phenyl, phenethyl or phenylmethyl; R_2 is phenylmethyl or propyl) utilizing a silyl substituted allylic carbonate of formula VV-2. Desilylation results in the compound of formula VV-4 (wherein, e.g., R_1 is phenyl, phenethyl or phenylmethyl; R_2 is phenylmethyl or propyl) and subsequent reduction results in the compound of formula VV-5 (wherein, e.g., R_1 is phenyl, phenethyl or phenylmethyl; R_2 is phenylmethyl or propyl).

CHART WW

This chart describes a generic procedure for the synthesis of the C-3 α branched 5,6-dihydropyrones by alkylation with 1,3-diphenyl allyl alcohol. Thus, boron trifluoride etherate catalyzed reaction of the compound of formula WW-1 (wherein, e.g., R_1 is phenyl, phenethyl or phenylmethyl; R_2 is propyl, phenylmethyl or 2-methylpropyl) with 1,3-diphenyl allyl alcohol (WW-2) provides compounds of the formula WW-3 (wherein, e.g., R_1 is phenyl, phenethyl or phenylmethyl; R_2 is propyl, phenylmethyl or 2-methylpropyl). Subsequent hydrogenation catalyzed by Pd/C provides the compound of formula WW-4 (wherein, e.g., R_1 is phenyl, phenethyl or phenylmethyl; R_2 is propyl, phenylmethyl or 2-methylpropyl).

CHART XX

This chart is a variation of Chart WW. The only change is that trans-stilbene oxide replaces 1,3-diphenyl allyl alcohol. This chart describes a generic procedure for the synthesis of C-3 α branched 5,6-dihydropyrones by alkylation with trans-stilbene oxide. Thus, boron trifluoride etherate catalyzed reaction of the compound of formula XX-1 (wherein, e.g., R_1 is phenethyl; R_2 is propyl) with trans-stilbene oxide (XX-2) provides compounds of formula XX-3 (wherein, e.g., R_1 is phenethyl; R_2 is propyl). Subsequent hydrogenation catalyzed by Pd/C provides the compound of formula XX-4 (wherein, e.g., R_1 is phenethyl; R_2 is propyl).

CHART YY

Racemic 3-phenylpentanoic acid (YY-4) is prepared from hydrogenation using Pd/C of YY-2, and followed by basic hydrolysis of ester YY-3. The ester YY-2 is prepared by an orthoester Claisen rearrangement on cinnamyl alcohol YY-1 using 1,1,1-triethoxyethane. Acid YY-4 is readily resolved by reacting the acid YY-4 with diethyl phosphorylchloride in the presence of triethylamine, yielding an activated acyl intermediate which is then treated with (S)- α -methylbenzyl amine to yield a mixture of YY-5 and YY-6. YY-5 is obtained diastereomerically pure as a crystalline solid (the other diastereomer YY-6 is in the mother liquors). Treatment of YY-5 with H_3PO_4 at 150-60°C then yields pure (R)-3-phenylpentanoic acid YY-7 (which is the same as CC-1). The (S)-3-Phenylpentanoic acid is obtained following the above procedures if (R)- α -methylbenzyl amine is used to form the diastereomeric amides of the racemic acid YY-4.

CHART ZZ

Diethyl malonate (ZZ-1) is alkylated with ethyl iodide to give compound of formula ZZ-2, which is further alkylated with benzyl bromide to give compound of formula ZZ-3 (Procedures in Organic Syntheses, Coll. VI:250). Hydrolysis of ZZ-3 gives the racemic acid ZZ-4. The optically active acids, ZZ-5 (which is the same as W-4) and ZZ-6 (which is the same as X-4), are obtained from fractional crystallization of the racemic acid ZZ-4 with either the R or the S isomer of α -methylbenzyl amine.

CHART AAA

This chart illustrates the Lewis acid catalyzed coupling reaction between 5,6-dihydro-6,6-disubstituted-2H-pyran-2-ones (AAA-1 wherein, e.g., R₁ is 2-methylpropyl, R₂ is phenylethyl) and benzhydrol (AAA-2) to provide 3-diphenylmethyl derivatives (AAA-3 wherein, e.g., R₁ is phenylethyl, R₂ is 2-methylpropyl).

CHART BBB

Acetic acid (BBB-1) is treated with two equivalents of lithium diisopropylamide in tetrahydrofuran. To that solution is added cyclopropane carboxaldehyde (commercially available). After aqueous workup, racemic BBB-2 is isolated. (R) BBB-2b and (S) BBB-2a are obtained from fraction crystallization of the racemic acid with either the R or S isomer of α -methylbenzyl amine, ephedrine, brucine, strychnine, quinine, cinchonidine, quinidine or cinchonine. Alternatively, aldol condensation using the Evan's strategy (J. Amer. Chem. Soc. (1981) 103, 2127) would also afford pure enantiomers BBB-2a and BBB-2b. BBB-2a is treated with triethylorthoacetate to yield BBB-3 (Helv. Chim. Acta. (1987) 70, 1320). Upon thermolysis of BBB-3, BBB-4 is obtained (Helv. Chim. Acta. (1987) 70, 1320). Treatment of BBB-4 with BBB-5 in the presence of Cuprous iodide (Tetrahedron Letters 1253 (1984)) gives BBB-6. Treatment of BBB-6 with oxalyl chloride in methylene chloride for several hours yields BBB-7. To a hot toluene solution of BBB-7 is added a toluene solution of triethylamine and BBB-8. The reaction is heated for several hours and the solvent is removed via evaporation when thin layer chromatography (silica gel, ethyl acetate) indicates complete consumption of BBB-8. The crude reaction is diluted with a 10/1 mixture of methanol/water followed by addition of sodium carbonate. This then affords BBB-9. Treatment of BBB-9 with a catalytic amount of p-toluenesulfonic acid and several equivalents of methanol in ether yields BBB-10. Treatment of a methylene chloride solution of BBB-10 with p-cyanobenzenesulfonylchloride in the presence of triethylamine affords BBB-11.

Alternately, treatment of BBB-3 with BBB-5 in the presence of Cuprous iodide (Tetrahedron Letters 1253 (1984)) gives BBB-12, which is the enantiomer of BBB-6, and when carried through the analogous steps as BBB-6 yields BBB-13.

Furthermore, BBB-14 and BBB-15 are substituted for BBB-4 and BBB-3 to prepare the corresponding ethyl stereoisomers.

CHART CCC

Ketone CCC-1 is treated with (carbethoxymethylene)triphenylphosphorane to yield unsaturated ester CCC-2. Reduction (Red-Al/CuBr; DIBAH/MeCu; NaBH₄/resin; NaBH₄/Cu₂Cl₂; ref. Reduction by the Alumino and Borohydrides in Organic Synthesis, J. Seyden-Penne, VCH Publishers, Inc. Lavoisier - Tec & Doc, 1991, p 156) of CCC-2 followed by ester hydrolysis yields CCC-3. (R) CCC-4a and (S) CCC-4b are obtained from fraction crystallization of the racemic acid CCC-3 with either the R or S isomer of α -methylbenzyl amine, ephedrine, brucine, strychnine, quinine, cinchonidine, quinidine or cinchonine. Alternatively, CCC-4a and CCC-4b are obtained via asymmetric reduction (Angew. Chem. Int. Ed. Engl. (1989) 28, 60) followed by basic hydrolysis. Following the protocol described in Chart BBB, CCC-6 is prepared.

CHART DDD

2-Thienylamine DDD-1 (commercially available) is treated with 2 equivalents of n-butyl lithium in ether at -78°C. After stirring at -78°C for 30 minutes the reaction temperature is raised to 0°C for 30 minutes followed by the addition of sulfur (fine powder). After aqueous workup, DDD-2 is isolated (J. Amer. Chem. Soc. (1955) 77, 5357, 5446; Org. Syn. Vol. VI, 979 (1988)). DDD-2 is treated with p-fluorophenylsulfonyl chloride in methylene chloride in the presence of triethylamine to yield DDD-3. DDD-3 is also available via first reacting DDD-1 with p-fluorobenzenesulfonylchloride followed by treatment of that intermediate with 2 equivalents of n-butyl lithium in ether followed by the addition of sulfur. Treatment of a mixture of DDD-3 and DDD-4 in ether with triethylamine affords DDD-5 (US Patent 4968815). Following the same procedure as found in Chart BBB, DDD-5 is converted to an acid chloride and reacted with (R) 2,2-dimethyl-6-(α -ethylphenethyl)-4H-1,3-dioxin-4-one to afford DDD-6.

As is apparent to those of ordinary skill in the art, the compounds of the present invention can occur in several diastereomeric forms, depending on the configuration around the asymmetric carbon atoms. All such diastereomeric forms are included within the scope of the present invention. Also, the compounds of the present invention can exist in several tautomeric forms, including the particular enol form as depicted in the Formula Chart below by formula I and the keto form of formula II and mixtures thereof. (For formulas I and II, the dashed line indicates that a double bond may be present or absent.) All such tautomeric forms are included within the scope of the present invention. For compounds of the present invention which are 4-hydroxy-pyran-2-ones of formula IV in the Formula Chart below, the enol form predominates. For compounds of the present invention which are 5,6-dihydro-4-hydroxy-pyran-2-ones of formula III in the Formula Chart below, a mixture of the enol and keto forms is commonly expected.

The compounds of the present invention may be in either the free form or the protected

form at one or more of the remaining (not previously protected) carboxyl, amino, hydroxy or other reactive groups. The protecting groups may be any of those known in the art. Examples of nitrogen and oxygen protecting groups are set forth in T.W. Greene, *Protecting Groups in Organic Synthesis*, Wiley, New York (1981); J.F.W. McOmie, ed., *Protective Groups in Organic Chemistry*, Plenum Press (1973); and J. Fuhrhop and G. Benzlin, *Organic Synthesis*, Verlag Chemie (1983). Included among the nitrogen protective groups are tert-butoxycarbonyl (BOC), benzyloxycarbonyl, acetyl, allyl, phthalyl, benzyl, benzoyl, trityl, and the like. Included among the ketone protective groups is 1,3-dioxalane.

The present invention provides for compounds of formula I or pharmacologically acceptable salts and/or hydrates thereof. Pharmacologically acceptable salts refers to those salts which would be readily apparent to a manufacturing pharmaceutical chemist to be equivalent to the parent compound in properties such as formulation, stability, patient acceptance and bioavailability. Examples of salts of the compounds of the present invention include acidic salts, such as sodium and potassium salts of the compounds of formula I, and basic salts, such as the hydrochloride salt of the compounds of formula I, wherein the R substituents contain a basic moiety.

The compounds of the present invention are useful for treating patients infected with human immunodeficiency virus (HIV) which results in acquired immunodeficiency syndrome (AIDS) and related diseases. For this indication, these compounds may be administered by oral, intranasal, transdermal, subcutaneous and parenteral (including intramuscular and intravenous) routes in doses of 0.1 mg to 100 mg/kg of body weight per day.

Those skilled in the art would know how to formulate the compounds of this invention, using pharmaceutically acceptable carriers, into appropriate pharmaceutical dosage forms. Examples of the dosage forms include oral formulations, such as tablets or capsules, or parenteral formulations, such as sterile solutions.

When the compounds in this invention are administered orally, an effective amount is from about 0.1 mg to 100 mg per kg of body weight per day. Either solid or fluid dosage forms can be prepared for oral administration. Solid compositions are prepared by mixing the compounds of this invention with conventional ingredients such as talc, magnesium stearate, dicalcium phosphate, magnesium aluminum silicate, calcium sulfate, starch, lactose, acacia, methyl cellulose, or functionally similar pharmaceutical diluents and carriers. Capsules are prepared by mixing the compounds of this invention with an inert pharmaceutical diluent or carrier and placing the mixture into an appropriately sized hard gelatin capsule. Soft gelatin capsules are prepared by machine encapsulation of a slurry of the compounds of this invention with an acceptable inert oil such as vegetable oil or light liquid petrolatum. Syrups are prepared by dissolving the compounds of this invention in an aqueous vehicle and adding sugar, aromatic

flavoring agents and preservatives. Elixirs are prepared using a hydroalcoholic vehicle such as ethanol, suitable sweeteners such as sugar or saccharin and an aromatic flavoring agent. Suspensions are prepared with an aqueous vehicle and a suspending agent such as acacia, tragacanth, or methyl cellulose.

5 When the compounds of this invention are administered parenterally, they can be given by injection or by intravenous infusion. An effective amount is from about 0.1 mg to 100 mg per kg of body weight per day. Parenteral solutions are prepared by dissolving the compounds of this invention in aqueous vehicle and filter sterilizing the solution before placing in a suitable sealable vial or ampule. Parenteral suspensions are prepared in substantially the same way
10 except a sterile suspension vehicle is used and the compounds of this invention are sterilized with ethylene oxide or suitable gas before it is suspended in the vehicle.

The exact route of administration, dose, or frequency of administration would be readily determined by those skilled in the art and is dependant on the age, weight, general physical condition, or other clinical symptoms specific to the patient to be treated.

15 Patients to be treated would be those individuals: 1) infected with one or more than one strain of a human immunodeficiency virus as determined by the presence of either measurable viral antibody or antigen in the serum and 2) having either an asymptomatic HIV infection or a symptomatic AIDS defining infection such as i) disseminated histoplasmosis, ii) isosporiasis, iii) bronchial and pulmonary candidiasis including pneumocystis pneumonia, iv) non-Hodgkin's
20 lymphoma, or v) Kaposi's sarcoma and being less than sixty years old; or having an absolute CD4+ lymphocyte count of less than $500/\text{mm}^3$ in the peripheral blood. Treatment would consist of maintaining an inhibitory level of the compounds of this invention in the patient at all times and would continue until the occurrence of a second symptomatic AIDS defining infection indicates alternate therapy is needed.

25 The HIV protease utility of representative compounds of the present invention has been demonstrated in the biological test described below:

IN VITRO HIV PROTEASE INHIBITORY ASSAY

The HIV protease screening assay is based on a fluorescently labeled substrate which can be resolved from nonlabeled cleavage product using avidin-polystyrene particles, 0.7-0.9
30 μm. The substrate is biotinylated at the amino terminal arginine and fluorescently labeled with fluorescein isothiocyanate (FITC) at the carboxyl terminal lysine. This assay has been employed to detect novel, nonpeptidic inhibitors of HIV-1 protease. Substrate (20 μl of 0.2 μM), sample (10 μl of desired concentraion), and enzyme (10 μl of 0.1 μM) are added to a 96 well pandex plate. The assay is run in 0.1 M sodium acetate buffer at pH 5.5 in the presence of 1.0 M
35 sodium chloride and 0.05% NP-40 and incubated in the dark for one hour at room temperature. Avidin coated polystyrene beads (40 μl of 0.1% (w/v)) are added and the incubation is

continued in the dark for an additional half hour. The labeled cleavage product is separated from the unreacted substrate via filtration and is read on the Idexx Screen Machine. The data are analyzed by appropriate computer algorithms to ascertain percent inhibition values.

The % inhibition values, and in some instances IC_{50} values or K_i values, of
5 representative compounds are listed in Tables I and II below.

Several compounds of the present invention, such as 3-(α -ethylbenzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one, were tested in known human cell lines, such as human T-cell lines, e.g., MT4 and H9, which were infected with HIV-1_{IIIb}, and certain of these compounds were further tested in peripheral blood mononuclear cells (PBMC), which were
10 infected with HIV-1_{JRCSE} (a clinical isolate). The compounds were found to inhibit retroviral replication.

Surprisingly and unexpectedly, the compounds of the present invention have also been found to decrease the size and weight of the prostate gland in male mammals. This is particularly unexpected in view of the fact that these compounds are structurally quite unlike
15 any known testosterone 5 α -reductase inhibitor. Also, the compounds of this invention may have a number of other uses, as described more fully below.

Thus, the present invention provides the use of compounds, such as 3-(α -Ethylbenzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one, for preventing and treating androgen-dependent diseases, including the prevention and treatment of human and animal prostate lesions, such as
20 benign prostatic hypertrophy and hyperplasia (nonneoplastic enlargements of the prostate) by, for example, maintaining and reducing the size of the prostate gland, and prostatic cancer in male mammals. Also, the present invention provides the use of these compounds to prevent and treat androgen-dependent skin diseases, such as alopecia, hirsutism, particularly female hirsutism, acne vulgaris and seborrhea, in mammals.

25 By "preventing" is meant avoiding the occurrence of a disease.

By "treating" is meant ameliorating or avoiding the effects of a disease.

By "maintaining" is meant keeping in an existing state.

By "mammals" is meant any warm-blooded vertebrate animal of the class *Mammalia* comprising humans and all other animals that nourish their young with milk secreted by
30 mammary glands and have the skins usually more or less covered with hair. Especially included are human beings, dogs and rats.

By "hypertrophy" is meant the enlargement or overgrowth of an organ or part due to an increase in size of its constituent cells.

By "hyperplasia" is meant the abnormal multiplication or increase in the number of
35 normal cells in normal arrangement in a tissue.

Accordingly, the present invention is also concerned with providing a method of

preventing or treating the androgen-dependent diseases of alopecia, hirsutism, acne vulgaris and seborrhea by topical administration, and a method of preventing or treating all of the above conditions as well as benign prostatic hypertrophy and prostate cancer, by topical or parenteral administration, of the compounds of the present invention. Thus, the present invention is
5 concerned with providing suitable topical and parenteral pharmaceutical formulations for use in the novel methods of treatment of the present invention.

The variety of therapeutic dosage forms for different modes of administration and their preparation are hereby incorporated by reference herein from the following: U.S. Patent 4,377,584, col. 10, line 52, through col. 11, line 31; U.S. Patent 4,760,071, col. 6, line 62,
10 through col. 7, line 42; and U.S. Patent 5,017,568, col. 28, lines 3-39.

The amount of the compound of formula I which is effective for the treatment of the above stated conditions ranges from 1 through 1000 mg/kg/day, with 50 through 400 mg/kg/day being preferred and 100 through 400 mg/kg/day being the most preferred. The exact therapeutic dosage form, mode and frequency of administration, and dosage would be readily determined by
15 those skilled in the art and is dependent on the age, weight, general physical condition or other clinical symptoms specific to the patient, human and other mammals, to be treated.

The following five (5) compounds of the present invention were tested in an *in vitro* testosterone 5 α -reductase inhibitor assay: 3-(α -Ethylbenzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one; 6-(1-Benzyl-propyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one; 3-
20 (α -Ethylbenzyl)-6-(α -ethylbenzyl)-4-hydroxy-2H-pyran-2-one; 3-(α -Ethylbenzyl)-6-phenethyl-4-hydroxy-2H-pyran-2-one; 4-Hydroxy-3-(1-phenylpropyl)-6-[1-[(tetrahydro-2H-pyran-3-yl)methyl]propyl]-2H-pyran-2-one. This assay is very similar to those described in the following references, except for the use of dog and rat prostates in place of human prostates: Proc. Natl. Acad. Sci. USA, Vol. 90: 5277-5281 (1993); J. Steroid. Biochem. Molec. Biol., Vol.
25 44, No. 2, pp. 121-131 (1993). All five (5) compounds had activity in this assay at a dose of at least 0.1 mM.

Therefore, and without wishing to be limited to a specific mechanism of action, it was concluded that these compounds and other related compounds of the present invention would be useful for preventing or treating androgen-dependent diseases, such as those described above.

30 The utility of representative compounds of the present invention has been demonstrated in the biological tests described below:

3-(α -Ethylbenzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one was further tested *in vivo* in a four-week oral drug safety and toxicity study in beagle dogs, described in Example 208 below. It was found that, during the conduct of the postdosing evaluation of data from this
35 study, there was a dose-related decrease in prostate size and weight in male dogs. Mean prostatic weights (n=3, 3 dogs in each of groups 1-5) are given in Table IV below. Light

microscopic examination of high dose and control testes, adrenals and pituitaries did not show drug-related changes.

In a repeat study (groups 6 and 7, of 4 dogs each) the results of which are also given in Table IV, 2/4 high dose dogs had lower absolute and relative prostate weights than did the controls, but decreases were marked only in 1/4 dogs.

As demonstrated in this *in vivo* test, the ability of 3-(α -Ethylbenzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one to reduce the size and weight of the prostate gland, particularly without significant effects on testes and other endocrine glands, indicates that this compound and related compounds of the present invention would be useful to prevent or treat androgen-dependent diseases, such as those described above, especially benign prostatic hypertrophy and hyperplasia in male mammals.

The following compounds of the present invention are preferred:

- 3-(α -ethylbenzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 3-([R]- α -ethylbenzyl)-4-hydroxy-6-([R]- α -ethylphenethyl)-2H-pyran-2-one;
- 3-([R]- α -ethylbenzyl)-4-hydroxy-6-([S]- α -ethylphenethyl)-2H-pyran-2-one;
- 3-([S]- α -ethylbenzyl)-4-hydroxy-6-([R]- α -ethylphenethyl)-2H-pyran-2-one;
- 3-([S]- α -ethylbenzyl)-4-hydroxy-6-([S]- α -ethylphenethyl)-2H-pyran-2-one;
- Sodium (3S,6R) 3-(α -ethylbenzyl)-6-(α -ethylphenethyl)-2H-pyran-2-one 4-oxide;
- N-(3-Cyclopropyl-{6-(1-ethyl-phenethyl)-4-hydroxy-2-oxo-2H-pyran-3-yl}-methyl)-phenyl)-3-(*tert*-butoxycarbonylamino)-propionamide;
- 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(1-(tetrahydro-furan-3-ylmethyl)-propyl)-pyran-2-one;
- 6-(1-(5-Chloro-thiophen-2-ylmethyl)-propyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one;
- 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(1-(tetrahydro-furan-2-ylmethyl)-propyl)-pyran-2-one;
- 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(1-tetrahydro-pyran-4-ylmethyl)-propyl)-pyran-2-one;
- 3-(Cyclopropyl-phenyl-methyl)-6-(1-furan-2-ylmethyl-propyl)-4-hydroxy-pyran-2-one;
- 3-(Cyclopropyl-phenyl-methyl)-6-(1-(1,3)dioxolan-2-ylmethyl-propyl)-4-hydroxy-pyran-2-one;
- 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(1-(tetrahydro-pyran-3-ylmethyl)-propyl)-pyran-2-one;
- 6-(4-Chloro-1-ethyl-butyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one;
- 6-(3-Chloro-1-ethyl-propyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one;
- 3-(Cyclopropyl-phenyl-methyl)-6-(1-ethyl-3-thiophen-3-yl-propyl)-4-hydroxy-pyran-2-

- one;
 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-[1-(tetrahydro-pyran-3-ylmethyl)-butyl]-
 pyran-2-one;
 3-(1-Benzyl-2-phenyl-ethyl)-6-(2-cyclopropyl-1-cyclopropylmethyl-ethyl)-4-hydroxy-
 5 pyran-2-one;
 6-(2-Cyclopropylmethyl-ethyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one;
 3-(Cyclopropyl-phenyl-methyl)-6-(1-ethyl-3-(2-methoxy-ethoxy)-propyl)-4-hydroxy-
 pyran-2-one;
 6-(1-Benzyl-3-(2-methoxy-ethoxy)-propyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-
 10 pyran-2-one;
 3-(Cyclopropylphenylmethyl)-4-hydroxy-6-[2-methyl-1-(phenylmethyl)propyl]-2H-pyran-
 2-one;
 3-(Cyclopropylphenylmethyl)-4-hydroxy-6-[2-methyl-1-[(tetrahydro-2H-pyran-3-
 yl)methyl]propyl]-2H-pyran-2-one;
 15 4-Hydroxy-3-(1-phenylpropyl)-6-[1-[(tetrahydro-2H-pyran-3-yl)methyl]propyl]-2H-pyran-
 2-one;
 3-(Cyclopropylphenylmethyl)-6-(1-ethyl-4,4,4-trifluorobutyl)-4-hydroxy-2H-pyran-2-one;
 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(α -ethyl-p-bromophenethyl)-2H-pyran-2-one;
 3-(1,3-Diphenyl-2-propenyl)-5,6-dihydro-4-hydroxy-6-(2-phenylethyl)-6-propyl-, (E)-2H-
 20 pyran-2-one;
 3-(1,3-Diphenyl-2-propyl)-5,6-dihydro-4-hydroxy-6-(2-phenylethyl)-6-propyl-, (E)-2H-
 pyran-2-one;
 5,6-Dihydro-4-hydroxy-6-(2-phenylethyl)-3-(1-phenyl-2-propenyl)-6-propyl-2H-pyran-2-
 one;
 25 5,6-Dihydro-4-hydroxy-6-(2-phenylethyl)-3-(1-phenylpropyl)-6-propyl-2H-pyran-2-one;
 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(α -ethyl-p-fluorophenethyl)-2H-pyran-2-one;
 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(α -ethyl- β -hydroxyphenethyl)-2H-pyran-2-one;
 3-(α -Cyclopropyl-*meta*-(phenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-
 2H-pyran-2-one;
 30 3-(α -Cyclopropyl-*meta*-(propylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-
 2H-pyran-2-one;
 3-(α -Cyclopropyl-*meta*-(E)-2-phenylethenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-
 4-hydroxy-2H-pyran-2-one;
 3-(α -Cyclopropyl-*meta*-(4-bromophenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-
 35 hydroxy-2H-pyran-2-one;
 3-(α -Cyclopropyl-*meta*-(4-cyanophenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-

- hydroxy-2H-pyran-2-one;
 3-(α -Cyclopropyl-*meta*-(4-methoxyphenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
 3-(α -cyclopropylbenzyl)-6-(1-propylbutyl)-4-hydroxy-2H-Pyran-2-one;
 5 5,6-Dihydro-4-hydroxy-6-(2-methylpropyl)-6-(2-phenylethyl)-3-(1-phenyl-2-propenyl)-2H-pyran-2-one;
 5,6-Dihydro-4-hydroxy-6-(2-methylpropyl)-6-(2-phenylethyl)-3-(1-phenylpropyl)-2H-pyran-2-one;
 3-(α -Cyclopropyl-*meta*-(*tert*-butyloxycarbonyl-L-alanyl-amino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
 10 3-(α -Cyclopropyl-*meta*-(N- α -*tert*-butyloxycarbonyl-N-im-p-toluenesulfonyl-L-histidyl-amino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
 3-(α -Cyclopropyl-*meta*-(4-chlorophenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
 15 3-(α -Cyclopropyl-*meta*-(N- α -*tert*-butyloxycarbonyl-L-histidyl-amino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
 3-(α -Cyclopropyl-*meta*-(ethylsulfonylamino)benzyl)-6-[1-cyclopropylmethyl-2-(tetrahydropyran-3-yl)ethyl]-4-hydroxy-2H-pyran-2-one;
 3-(α -Cyclopropyl-*meta*-(4-methylphenylsulfonylamino)benzyl)-6-[1-cyclopropylmethyl-2-(tetrahydropyran-3-yl)ethyl]-4-hydroxy-2H-pyran-2-one;
 20 3-(α -Cyclopropyl-*meta*-(4-methylphenylsulfonylamino)benzyl)-6-(α -ethyl-phenethyl)-4-hydroxy-2H-pyran-2-one;
 3-(α -Cyclopropyl-*meta*-(ethylsulfonylamino)benzyl)-6-(α -ethyl-phenethyl)-4-hydroxy-2H-pyran-2-one;
 25 3-(α -Cyclopropyl-[5-(methoxymethoxy-methyl)-thiophen-2-yl]-methyl)-5,6-dihydro-4-hydroxy-6-(2-phenylethyl)-6-propyl-2H-pyran-2-one; and
 5,6-Dihydro-3-diphenylmethyl-4-hydroxy-6-(3-phenylpropyl)-6-propyl-2H-pyran-2-one.
 The most preferred compounds of the present invention are the following:
 3-(α -ethylbenzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-Pyran-2-one;
 30 3-([S]- α -ethylbenzyl)-4-hydroxy-6-([R]- α -ethylphenethyl)-2H-pyran-2-one;
 Sodium (3S,6R) 3-(α -ethylbenzyl)-6-(α -ethylphenethyl)-2H-pyran-2-one 4-oxide;
 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(1-(tetrahydro-furan-2-ylmethyl)-propyl)-pyran-2-one;
 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(1-(tetrahydro-pyran-3-ylmethyl)-propyl)-pyran-2-one;
 35 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-[1-(tetrahydro-pyran-3-ylmethyl)-butyl]-

pyran-2-one;

3-(1-Benzyl-2-phenyl-ethyl)-6-(2-cyclopropyl-1-cyclopropylmethyl-ethyl)-4-hydroxy-
pyran-2-one;

6-(2-Cyclopropylmethyl-ethyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one;

5 3-(Cyclopropylphenylmethyl)-4-hydroxy-6-[2-methyl-1-[(tetrahydro-2H-pyran-3-
yl)methyl]propyl]-2H-pyran-2-one;

3-(1,3-Diphenyl-2-propyl)-5,6-dihydro-4-hydroxy-6-(2-phenylethyl)-6-propyl-, (E)-2H-
pyran-2-one;

10 5,6-Dihydro-4-hydroxy-6-(2-phenylethyl)-3-(1-phenyl-2-propenyl)-6-propyl-2H-pyran-2-
one;

5,6-Dihydro-4-hydroxy-6-(2-phenylethyl)-3-(1-phenylpropyl)-6-propyl-2H-pyran-2-one;

3-(α -cyclopropylbenzyl)-4-hydroxy-6-(α -ethyl- β -hydroxyphenethyl)-2H-pyran-2-one;

3-(α -Cyclopropyl-*meta*-(phenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-
2H-pyran-2-one;

15 3-(α -Cyclopropyl-*meta*-((E)-2-phenylethenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-
4-hydroxy-2H-pyran-2-one;

3-(α -Cyclopropyl-*meta*-(4-bromophenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-
hydroxy-2H-pyran-2-one;

3-(α -Cyclopropyl-*meta*-(4-cyanophenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-
20 hydroxy-2H-pyran-2-one;

3-(α -Cyclopropyl-*meta*-(4-methoxyphenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-
hydroxy-2H-pyran-2-one;

5,6-Dihydro-4-hydroxy-6-(2-methylpropyl)-6-(2-phenylethyl)-3-(1-phenyl-2-propenyl)-
2H-pyran-2-one;

25 5,6-Dihydro-4-hydroxy-6-(2-methylpropyl)-6-(2-phenylethyl)-3-(1-phenylpropyl)-2H-
pyran-2-one;

3-(α -Cyclopropyl-*meta*-(*tert*-butoxycarbonyl-L-alanyl-amino)benzyl)-6-(α -
ethylphenethyl)-4-hydroxy-2H-pyran-2-one;

3-(α -Cyclopropyl-*meta*-(N- α -*tert*-butoxycarbonyl-N-im-p-toluenesulfonyl-L-
30 histidyl-amino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;

3-(α -Cyclopropyl-*meta*-(4-chlorophenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-
hydroxy-2H-pyran-2-one;

3-(α -Cyclopropyl-*meta*-(N- α -*tert*-butoxycarbonyl-L-histidyl-amino)benzyl)-6-(α -
ethylphenethyl)-4-hydroxy-2H-pyran-2-one;

35 3-(α -Cyclopropyl-*meta*-(ethylsulfonylamino)benzyl)-6-[1-cyclopropylmethyl-2-

-62-

(tetrahydropyran-3-yl)ethyl]-4-hydroxy-2H-pyran-2-one;

3-(α -Cyclopropyl-*meta*-(4-methylphenylsulfonylamino)benzyl-6-[1-cyclopropylmethyl-2-(tetrahydropyran-3-yl)ethyl]-4-hydroxy-2H-pyran-2-one;

3-(α -Cyclopropyl-*meta*-(4-methylphenylsulfonylamino)benzyl-6-(α -ethyl-phenethyl)-4-hydroxy-2H-pyran-2-one;

3-(α -Cyclopropyl-*meta*-(ethylsulfonylamino)benzyl-6-(α -ethyl-phenethyl)-4-hydroxy-2H-pyran-2-one;

3-(α -Cyclopropyl-[5-(methoxymethoxy-methyl)-thiophen-2-yl]-methyl)-5,6-dihydro-4-hydroxy-6-(2-phenylethyl)-6-propyl-2H-pyran-2-one; and

5,6-Dihydro-3-diphenylmethyl-4-hydroxy-6-(3-phenylpropyl)-6-propyl-2H-pyran-2-one.

For the treatment of androgen-dependent diseases the following compounds of the present invention are preferred:

3-(α -Ethylbenzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;

6-(1-Benzyl-propyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one;

3-(α -Ethylbenzyl)-6-(α -ethylbenzyl)-4-hydroxy-2H-pyran-2-one;

3-(α -Ethylbenzyl)-6-phenethyl-4-hydroxy-2H-pyran-2-one; and

4-Hydroxy-3-(1-phenylpropyl)-6-[(tetrahydro-2H-pyran-3-yl)methyl]propyl]-2H-pyran-2-one.

The most preferred compound of the present invention for this use is 3-(α -Ethylbenzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

In the Preparations and Examples below and throughout this document:

$^{\circ}\text{C}$ is degrees Centigrade.

M is molar (concentration).

N is normal (concentration).

mL is milliliter.

mg is milligram.

mmHg is millimeter of mercury.

$^1\text{H-NMR}$ is proton nuclear magnetic resonance spectrum.

$^{13}\text{C-NMR}$ is carbon nuclear magnetic resonance spectrum.

δ is chemical shift (parts per million) relative to TMS.

CDCl_3 is deuterio-chloroform.

CD_3OD is deuterio-methanol.

FAB MS is fast-atom-bombardment mass spectroscopy.

HRMS is high-resolution mass spectroscopy.

Anal. is analytical data.

-63-

Pd/C is palladium on charcoal.

THF is tetrahydrofuran.

The following Preparations and Examples illustrate the present invention:

PREPARATION 1 Ethyl 5-phenyl-3,5-dioxopentanoate (Formula A-3: X is CH) Refer to Chart A.

To a suspension of 50 mg potassium hydride in 1 mL of dry tetrahydrofuran is added dropwise 130 mg of ethyl acetoacetate (A-1) at 0 °C, followed by addition of 0.7 mL of 1.6 M n-butyl lithium-hexane solution. To the resulting yellow reaction mixture is then added 150 mg of ethyl benzoate (A-2: X is CH), and stirred for another 5 min. The reaction is quenched with 0.5 mL glacial acetic acid, and then diluted with 1 mL water. The tetrahydrofuran is removed under reduced pressure and the aqueous layer is extracted with methylene chloride (2 X 5 mL). The combined organic layers are washed with water (2 mL), dried (magnesium sulfate), and then concentrated. The residue is purified by flash column chromatography (0 to 30 % ethyl acetate in hexane) to give 201 mg of the title product as colorless oil.

Physical characteristics are as follows:

¹H-NMR (CDCl₃) δ 1.29, 3.48, 4.22, 6.30, 7.47, 7.87, 15.81.

¹³C-NMR (CDCl₃) δ 13.8, 45.6, 61.2, 96.5, 126.8, 128.4, 132.4, 133.8, 167.3, 182.3, 189.1.

PREPARATION 2 4-Hydroxy-6-phenyl-2-pyrone (Formula A-4: X is CH) Refer to Chart A.

The title product of Preparation 1 (700 mg) is heated at 120 °C under reduced pressure (1 mm Hg) for 10 h. The resulting brownish cake is washed with diethyl ether, dried under reduced pressure to give 411 mg of the title product as white solid.

Physical characteristics are as follows:

¹H-NMR (CDCl₃) δ 5.40, 6.78, 7.53, 7.85.

EXAMPLE 1 4-Hydroxy-6-phenyl-3-(1'-phenyl-propyl)-2-pyrone; also named as 3-(α-ethylbenzyl)-4-hydroxy-6-phenyl-2H-Pyran-2-one (Formula A-5: X is CH, R is ethyl) Refer to Chart A.

To a solution of 94 mg of the title product of Preparation 2 and 104 mg of (±)-1-phenyl-1-propanol in 3 mL of dioxane is added 0.3 mL of boron trifluoride - diethyl ether at room temperature and allowed to stir for 10 h, and then is quenched with 1 mL of water. The reaction mixture is extracted with methylene chloride (3 X 5 mL) and the combined organic layers are washed with water (2 X 3 mL), brine (3 mL), dried (sodium sulfate) and then concentrated. The residue is purified by column chromatography (20 to 80 % ethyl acetate in hexane) to give 37.5 mg of the title product as a tan solid.

Physical characteristics are as follows:

¹H-NMR (CDCl₃ / CD₃OD) δ 0.94, 2.17, 2.35, 4.05, 4.23, 6.55, 7.17, 7.26, 7.42, 7.50.

7.75.

^{13}C -NMR ($\text{CDCl}_3 / \text{CD}_3\text{OD}$) δ 12.4, 23.8, 41.8, 97.7, 106.1, 124.9, 125.5, 127.5, 127.8, 128.4, 130.2, 130.9, 143.7, 158.0, 165.8.

FAB MS $[\text{M}]^+ = 306$.

PREPARATION 3 Ethyl 6-phenyl-3,5-dioxohexanoate (Formula B-3: n is 1) Refer to Chart B.

To a suspension of 580 mg potassium hydride in 15.0 mL of tetrahydrofuran is added 1.82 g of ethyl acetoacetate (B-1) at 0 °C and stirred for 30 min, then is added 9.0 mL of 1.6 M n-butyl lithium-hexane solution and stirred 1 h at 0 °C. To the reaction mixture is added 2.30 g of ethyl phenylacetate (B-2: n is 1) which results in precipitation, and therefore additional 50 mL of tetrahydrofuran is added. After stirring for 12 h at room temperature, the reaction is quenched with 10 mL of glacial acetic acid. The tetrahydrofuran is removed under reduced pressure and the aqueous layer is extracted with ethyl acetate (3 X 30 mL). The combined organic layers are washed with water (3 X 10 mL), brine (10 mL), dried (sodium sulfate) and then concentrated. The residue is then purified by flash column chromatography (10 % ethyl acetate in hexane) to afford 1.03 g of the title product as a light yellow oil.

Physical characteristics are as follows:

^1H -NMR (CDCl_3) δ 1.22, 2.18, 3.24, 3.40, 3.54, 3.59, 4.16, 7.22.

PREPARATION 4 Ethyl 7-phenyl-3,5-dioxoheptanoate (Formula B-3: n is 2) Refer to Chart B.

To a suspension of 580 mg of potassium hydride in 15.0 mL of tetrahydrofuran is added 1.82 g of ethyl acetoacetate (B-1) at 0 °C and stirred for 30 min, then is added 9.0 mL of 1.6 M n-butyl lithium-hexane solution and stirred 1 h at 0 °C. To the reaction mixture is added 2.49 g of ethyl dihydrocinnamate (B-2: n is 2) which results in precipitation, and therefore additional 50 mL of tetrahydrofuran is added. After stirring for 12 h at room temperature, the reaction is quenched with 10 mL of glacial acetic acid. The tetrahydrofuran is removed under reduced pressure and the aqueous layer is extracted with ethyl acetate (30 mL X 3). The combined organic layers are washed with water (3 X 10 mL), brine (10 mL), dried (sodium sulfate) and then concentrated. The residue is then purified by flash column chromatography (10 % ethyl acetate in hexane) to afford 718 mg of the title product as a light yellow oil.

Physical characteristics are as follows:

^1H -NMR (CDCl_3) δ 1.27, 2.28, 2.63, 2.88, 2.95, 3.31, 3.43, 4.19, 7.23.

PREPARATION 5 6-Benzyl-4-hydroxy-2-pyrone (Formula B-4: n is 1) Refer to Chart B.

The title product of Preparation 3 (510 mg) is heated at 100 °C under reduced pressure (1 mm Hg) for 16 h. The resulting white solid is washed with diethyl ether (10 mL), dried under reduced pressure to give 226 mg of the title product as white solid.

Physical characteristics are as follows:

$^1\text{H-NMR}$ (CD_3OD) δ 3.80, 5.32, 5.90, 7.29.

$^{13}\text{C-NMR}$ (CD_3OD) δ 40.6, 89.9, 102.3, 128.3, 129.9, 130.3, 136.8, 167.3, 168.2,

173.3.

5 FAB MS $[\text{M}]^+ = 202$.

PREPARATION 6 4-Hydroxy-6-phenethyl-2-pyrone (Formula B-4: n is 2) Refer to Chart B.

The title product of Preparation 4 (718 mg) is heated at 100 °C under reduced pressure (1 mm Hg) for 16 h. The resulting white solid is washed with diethyl ether (10 mL), dried under reduced pressure to give 346 mg of the title product as white solid.

10 Physical characteristics are as follows:

$^1\text{H-NMR}$ (CD_3OD) δ 2.73, 2.90, 5.34, 5.86, 7.20.

$^{13}\text{C-NMR}$ (CD_3OD) δ 33.8, 36.4, 89.9, 102.2, 127.4, 129.4, 129.6, 141.4, 167.3, 168.4,

173.3.

FAB MS $[\text{M}]^+ = 216$.

15 EXAMPLE 2 6-Benzyl-4-hydroxy-3-(1'-phenylpropyl)-2-pyrone; also named as 6-benzyl-3-(α -ethylbenzyl)-4-hydroxy-2H-Pyran-2-one (Formula B-5: n is 1) Refer to Chart B.

A mixture of the title product of Preparation 5 (21 mg) and (\pm)-1-bromo-1-phenylpropane (0.2 mL) are heated at 100 °C for 16 h. The crude reaction mixture is purified by flash column chromatography (10 to 30 % ethyl acetate in hexane) to give 11.2 mg of the title product as yellow solid.

Physical characteristics are as follows:

$^1\text{H-NMR}$ (CDCl_3) δ 0.96, 2.17, 3.80, 4.24, 5.93, 7.15-7.45.

25 EXAMPLE 3 4-Hydroxy-6-phenethyl-3-(1'-phenylpropyl)-2-pyrone; also named as 3-(α -ethylbenzyl)-6-phenethyl-4-hydroxy-2H-Pyran-2-one (Formula B-5: n is 2) Refer to Chart B.

A mixture of 22 mg of title product of Preparation 6 and 0.2 mL (\pm)-1-bromo-1-phenylpropane are heated at 100 °C for 16 h. The crude reaction mixture is purified by flash column chromatography (10 to 30 % ethyl acetate in hexane) to give 14 mg of the title product as yellow solid.

Physical characteristics are as follows:

$^1\text{H-NMR}$ (CDCl_3) δ 0.96, 2.17, 2.67, 2.89, 4.25, 5.93, 7.10-7.45.

FAB MS $[\text{M}]^+ = 334$.

PREPARATION 7 1-(4'-Bromophenyl)-butanol (Formula C-2: R is OH) Refer to Chart C.

35 To a solution of 1.90 g of 4-bromobenzaldehyde (C-1) in 20 mL of tetrahydrofuran at 0 °C is added 7.5 mL of 2 M propylmagnesium bromide-tetrahydrofuran solution and stirred for 2

- h. The reaction is quenched with 10 mL saturated ammonium chloride solution and 10 mL of water. The aqueous layer is extracted with diethyl ether (3 X 30 mL) and the combined organic layers are washed with brine (20 mL), dried (sodium sulfate), and then concentrated under reduced pressure. The residue is purified by flash column chromatography (5 % ethyl acetate in hexane) to give 1.97 g of the title product as a colorless oil.

Physical characteristics are as follows:

$^1\text{H-NMR}$ (CDCl_3) δ 0.93, 1.26-1.42, 1.59-1.76, 4.64, 7.21, 7.46.

PREPARATION 8 1-Bromo-1-(4'-bromophenyl)-butane (Formula C-2: R is Br) Refer to Chart C.

- To a solution of 229 mg of title product of Preparation 7 in 2 mL of diethyl ether is added 2 mL of 48 % hydrobromic acid at room temperature and then stirred for 72 h. The aqueous layer is extracted with diethyl ether (3 X 5 mL) and the combined organic layers are treated with excess solid sodium bicarbonate. After filtration, the organic is concentrated under reduced pressure to give 135 mg of the title product and is used without any further purification.

- Physical characteristics are as follows:

$^1\text{H-NMR}$ (CDCl_3) δ 0.93, 1.30-1.38, 1.45-1.48, 2.01-2.13, 2.18-2.26, 4.91, 7.25, 7.47.

EXAMPLE 4 3-[1'-(4"-Bromophenyl)-butyl]-4-hydroxy-6-phenethyl-2-pyrone; also named as 4-hydroxy-6-phenethyl-3-(.alpha.-propyl-p-bromobenzyl)-2H-Pyran-2-one (Formula C-4) Refer to Chart C.

- A mixture of 22 mg of title product of Preparation 6 and 115 mg title product of Preparation 8 in 1 mL toluene is refluxed for 16 h. The crude mixture is then purified by gravity column chromatography (10-60 % ethyl acetate in hexane) to give 13.9 mg of the title product as a yellow solid.

Physical characteristics are as follows:

- $^1\text{H-NMR}$ (CDCl_3) δ 0.92, 1.87-1.95, 2.27-2.35, 2.67, 2.89, 4.64, 5.86, 7.26, 7.53, 7.71.

FAB MS $[M]^+ = 426$.

PREPARATION 9 4-O-Cinnamyl-4-hydroxy-6-methyl-2-pyrone (Formula D-2) Refer to Chart D.

- To a solution of 2.522 g of 4-hydroxy-6-methyl-2-pyrone (D-1) in 20 mL of dimethylformamide is added 2.764 g of potassium carbonate at room temperature. The resulting suspension is heated at 90 °C for 1 h, and is added 3.942 g of cinnamyl bromide. After stirring at 90 °C for 12 h, the reaction is quenched with 10 % acetic acid (5 mL). The dimethylformamide is removed under reduced pressure and the aqueous is extracted with ethyl acetate (3 x 30 mL). The combined organic layers are layer concentrated, the residue is purified by flash column chromatography (10 to 30 % ethyl acetate in hexane) to give 3.970 g of the title product.

-67-

Physical characteristics are as follows:

$^1\text{H-NMR}$ (CDCl_3) δ 2.21, 4.65, 5.46, 5.82, 6.32, 6.72, 7.24- 7.42.

$^{13}\text{C-NMR}$ (CDCl_3) δ 19.8, 26.7, 69.2, 88.1, 100.4, 121.4, 126.0, 126.6, 128.3, 128.4, 128.6, 134.9.

5 $\text{FAB-MS } [M-1]^+ = 241$. Anal. Found: C, 76.27; H, 5.74.

PREPARATION 10 4-Hydroxy-6-methyl-3-(1'-phenyl-2'-propenyl)-2-pyrone (Formula D-3)

Refer to Chart D.

A solution of 968 mg of the title product of Preparation 9 in toluene (10 mL) is refluxed for 8 h. The toluene is removed under reduced pressure and the residue is purified by flash
10 column chromatography (50 to 80 % ethyl acetate in hexane) to give 817 mg of the title product.

Physical characteristics are as follows:

$^1\text{H-NMR}$ (CDCl_3 / CD_3OD) δ 2.15, 4.97, 5.14, 5.89, 6.53, 7.15-7.31.

$^{13}\text{C-NMR}$ (CDCl_3 / CD_3OD) δ 19.3, 43.9, 48.9, 100.7, 104.0, 115.8, 126.8, 127.4,
15 127.8, 137.7, 142.0, 160.5, 166.2.

$\text{FAB-MS } [M]^+ = 242$. Anal. Found: C, 73.92; H, 5.80.

This compound was also found to have HIV activity.

PREPARATION 11 4-Hydroxy-6-methyl-3-(1'-phenyl-propyl)-2-pyrone (Formula D-4) Refer
to Chart D.

20 A mixture of 2.48 g of the title product of Preparation 10 and 100 mg of 10% Pd/C in methanol (50 mL) are shaken for 10 h at room temperature under the hydrogen (30 psi) atmosphere. The catalyst is filtered through Celite and methanol is removed under reduced pressure to give 2.501 g of the title product as a white solid.

Physical characteristics are as follows:

25 $^1\text{H-NMR}$ (CDCl_3) δ 0.95, 2.12, 2.18, 2.32, 4.24, 6.13, 7.22, 7.47.

$\text{FAB MS } [M]^+ = 244$.

EXAMPLE 5 4-Hydroxy-6-phenethyl-3-(1'-phenylpropyl)-2-pyrone; also named as 3-(α -ethylbenzyl)-6-phenethyl-4-hydroxy-2H-Pyran-2-one (Formula D-4) Refer to
Chart D.

30 To a solution of 61 mg diisopropylamine in THF (2 mL) is added 0.375 mL 1.6 M n-butyl lithium-hexane solution at -20°C and stirred 30 min, then is added 49 mg of the title product of Preparation 11 in tetrahydrofuran (3 mL). After stirring at -20°C for 30 min, the reaction mixture is added 34 mg of benzyl bromide and allowed to stir for additional 30 min, then is quenched with 2 N hydrochloric acid (0.5 mL). The tetrahydrofuran is removed under
35 reduced pressure and the aqueous layer is extracted with ethyl acetate (3 x 5 mL). The combined organic layers are dried (sodium sulfate), concentrated and the residue is purified by

gravity column chromatography (20 to 60 % ethyl acetate in hexane) to give 53 mg of the title product as white solid.

Physical characteristics are as follows:

¹H-NMR spectrum is identical to that given in Example 3.

- 5 EXAMPLE 6 6-(4'-Bromophenethyl)-4-hydroxy-3-(1'-phenylpropyl)-2-pyrone; also named as 6-(p-bromophenethyl)-3-(.alpha.-ethylbenzyl)-4-hydroxy-2H-Pyran-2-one (Formula E-2: R is 4-bromo-phenyl-CH₂-) Refer to Chart E.

To a solution of 61 mg diisopropylamine in THF (2 mL) is added 0.375 mL 1.6 M n-butyl lithium-hexane solution at -20 °C and stirred 30 min, then is added 49 mg of E-1 in 10 tetrahydrofuran (3 mL). After stirring at -20 °C for 30 min, the reaction mixture is added 50 mg of 4-bromobenzyl bromide and allowed to stir for additional 30 min, then is quenched with 2 N hydrochloric acid (0.5 mL). The tetrahydrofuran is removed under reduced pressure and the aqueous layer is extracted with ethyl acetate (3 x 5 mL). The combined organic layers are dried (sodium sulfate), concentrated and the residue is purified by gravity column chromatography (20 15 to 60 % ethyl acetate in hexane) to give 23 mg of the title product as white solid.

Physical characteristics are as follows:

¹H-NMR (CD₃OD) δ 0.92, 2.12-2.26, 2.60, 2.80, 4.22, 6.00, 6.90-7.51.

HRMS found 413.0674.

Anal. Found: C, 64.04; H, 5.28.

- 20 EXAMPLE 7 6-(2'-Fluorophenethyl)-4-hydroxy-3-(1'-phenylpropyl)-2-pyrone; also named as 3-(.alpha.-ethylbenzyl)-6-(o-fluorophenethyl)-4-hydroxy-2H-Pyran-2-one (Formula E-2: R is 2-fluoro-phenyl-CH₂-) Refer to Chart E.

To a solution of 61 mg diisopropylamine in tetrahydrofuran (2 mL) is added 0.375 mL 1.6 M n-butyl lithium-hexane solution at -20 °C and stirred 30 min, then is added 49 mg of E-1 25 in tetrahydrofuran (3 mL). After stirring at -20 °C for 30 min, the reaction mixture is added 38 mg of 2-fluorobenzyl bromide and allowed to stir for additional 30 min, then is quenched with 2 N hydrochloric acid (0.5 mL). The tetrahydrofuran is removed under reduced pressure and the aqueous layer is extracted with ethyl acetate (3 x 5 mL). The combined organic layers are dried (sodium sulfate), concentrated and the residue is purified by gravity column chromatography (20 30 to 60 % ethyl acetate in hexane) to give 6.1 mg of the title product as white solid.

Physical characteristics are as follows:

¹H-NMR (CDCl₃) δ 0.97, 2.16, 2.69, 2.96, 4.24,, 5.80, 7.02-7.45.

FAB-MS [M]⁺ = 352.

- 35 EXAMPLE 8 4-Hydroxy-3-(1'-phenylpropyl)-6-(3'-phenylpropyl)-2-pyrone; also named as 3-(.alpha.-ethylbenzyl)-4-hydroxy-6-(3-phenylpropyl)-2H-Pyran-2-one (Formula E-2: R is phenyl-CH₂CH₂-) Refer to Chart E.

To a solution of 49 mg of E-1 in tetrahydrofuran (2 mL) is added 0.31 mL 1.6 M n-butyl lithium-hexane solution at -20 °C and stirred 30 min, then is added 37 mg of (2-bromoethyl)benzene in tetrahydrofuran (3 mL). After stirring at -20 °C for 30 min, the reaction mixture is quenched with 2 N hydrochloric acid (0.5 mL). The tetrahydrofuran is removed under reduced pressure and the aqueous layer is extracted with ethyl acetate (3 x 5 mL). The combined organic layers are dried (sodium sulfate), concentrated and the residue is purified by gravity column chromatography (20 to 60 % ethyl acetate in hexane) to give 21.3 mg of the title product as white solid.

Physical characteristics are as follows:

¹H-NMR (CDCl₃) δ 0.93, 1.87, 2.17, 2.35, 2.59, 4.23, 5.99, 7.08-7.46, 9.55.

FAB-MS [M]⁺ = 348.

EXAMPLE 9 4-Hydroxy-3-(1'-phenylpropyl)-6-propyl-2-pyrone; also named as 3-(.alpha.-ethylbenzyl)-4-hydroxy-6-propyl-2H-Pyran-2-one (Formula E-2: R is ethyl)

Refer to Chart E.

To a solution of 122 mg of E-1 in tetrahydrofuran (4 mL) is added 0.67 mL of 1.6 M n-butyl lithium-hexane solution at -20 °C and stirred 30 min, then is added 78 mg of iodoethane in tetrahydrofuran (6 mL). After stirring at -20 °C for 30 min, the reaction mixture is quenched with 2 N hydrochloric acid (0.5 mL). The tetrahydrofuran is removed under reduced pressure and the aqueous layer is extracted with ethyl acetate (3 X 5 mL). The combined organic layers are dried (sodium sulfate), concentrated and the residue is purified by gravity column chromatography (20 to 60 % ethyl acetate in hexane) to give 39 mg of the title product as white solid.

Physical characteristics are as follows:

¹H-NMR (CD₃OD) δ 0.90-1.05, 1.60, 2.14-2.37, 4.24, 6.00, 7.18-7.48.

FAB-MS [M]⁺ = 372.

EXAMPLE 10 6-Allyl-4-hydroxy-3-(1'-phenylpropyl)-2-pyrone; also named as 3-(.alpha.-ethylbenzyl)-4-hydroxy-6-(3-butenyl)-2H-Pyran-2-one (Formula E-2: R is CH₂=CHCH₂-) Refer to Chart E.

To a solution of 61 mg of diisopropylamine in tetrahydrofuran (2 mL) is added 0.94 mL of 1.6 M n-butyl lithium-hexane solution at -20 °C and stirred 30 min, then is added 122 mg of E-1 in tetrahydrofuran (3 mL). After stirring at -20 °C for 30 min, the reaction mixture is added 61 mg of allyl bromide and allowed to stir for additional 30 min, then is quenched with 2 N hydrochloric acid. The tetrahydrofuran is removed under reduced pressure and the aqueous layer is extracted with ethyl acetate (3 X 5 mL). The combined organic layers are dried (sodium sulfate), concentrated and the residue is purified by gravity column chromatography (10 to 40 % ethyl acetate in hexane) to give 39 mg of an inseparable mixture (3 : 1) of the title

-70-

product and 6,6-diallyl-4-hydroxy-3-(1'-phenylpropyl)-2-pyrone.

Physical characteristics are as follows:

FAB-MS $[M]^+ = 324 \text{ \& } 364$.

EXAMPLE 11 3-(.alpha.-ethylbenzyl)-4-hydroxy-6-[[[(phenylamino)carbonyl]methyl]-2H-Pyran-

5 2-one (Formula F-2) Refer to Chart F.

To a solution of 304 mg diisopropylamine in tetrahydrofuran (5 mL) is added 1.7 mL of 1.6 M n-butyl lithium-hexane solution at -20 °C. The resulting lithium diisopropylamide solution is stirred for 30 min then is added 220 mg of F-1 in tetrahydrofuran (5 mL), the solution turns deep red color instantaneously. The reaction mixture is added 119 mg of phenyl isocyanate and stirred at -20 °C for 1 h, at 0 °C for 2 h, then is quenched with 2 N hydrochloric acid (3 mL). The tetrahydrofuran is removed under reduced pressure, the aqueous layer is extracted with ethyl acetate (3 x 10 mL). The combined organic layers are washed with 1 N hydrochloric acid (5 mL), water (5 mL), dried (sodium sulfate), concentrated. The residue is then purified by gravity column chromatography (2 to 5 % methanol in methylene chloride) to give 247.7 mg.

Physical characteristics are as follows:

$^1\text{H-NMR}$ (CD_3OD) δ 0.88, 2.08, 2.25, 3.57, 4.12, 6.19, 7.09-7.51.

$^{13}\text{C-NMR}$ (CD_3OD) δ 10.1, 22.1, 39.2, 40.3, 100.6, 103.8, 118.2, 122.5, 123.8, 125.8, 126.0, 126.8, 136.0, 142.3, 155.8, 165.8, 164.5, 1647.

20 HRMS found 363.1470.

Anal. Found: C, 71.20; H, 5.71; N, 3.70.

EXAMPLE 12 4-Hydroxy-3-(1'-phenyl-2'-propenyl)-6-propyl-2-pyrone; also named as 4-

hydroxy-6-phenethyl-3-(.alpha.-vinylbenzyl)-2H-Pyran-2-one (Formula G-2)

Refer to Chart G.

25 To a solution of 121 mg of G-1 in tetrahydrofuran (4 mL) is added 0.67 mL of 1.6 M n-butyl lithium-hexane solution at -20 °C and stirred 30 min, then is added 86 mg of benzyl bromide in tetrahydrofuran (6 mL). After stirring at -20 °C for 30 min, the reaction mixture is quenched with 2 N hydrochloric acid (0.5 mL). The tetrahydrofuran is removed under reduced pressure and the aqueous layer is extracted with ethyl acetate (3 X 5 mL). The combined organic layers are dried (sodium sulfate), concentrated and the residue is purified by gravity column chromatography (10 to 40 % ethyl acetate in hexane) to give 26.9 mg of the title product as white solid.

Physical characteristics are as follows:

$^1\text{HNMR}$ (CDCl_3) δ 2.05, 2.71, 2.93, 5.09, 5.30, 5.90, 6.47, 7.13-7.53.

35 FABMS $[M]^+ = 332$.

EXAMPLE 13 6-(1'-Benzyl-propyl)-4-hydroxy-3-(1'-phenyl-propyl)-2-pyrone; also named as 3-

(.alpha.-ethylbenzyl)-6-(.alpha.ethylphenethyl)-4-hydroxy-2H-Pyran-2-one

(Formula H-4: R₁ is -CH₂-phenyl; R₂ is ethyl) Refer to Chart H.

To a solution of 244 mg of H-3 and 101 mg of diisopropylamine in tetrahydrofuran (25 mL) is added 1.88 mL of 1.6 M n-butyl lithium-hexane solution at 0 °C and allowed to stir for 10 min. To the reaction is added 156 mg of iodoethane and stirred for 10 min, then is added 171 mg of benzyl bromide. The reaction mixture is stirred at 0 °C for 2 h, then is quenched with 2 N hydrochloric acid (2 mL) and water (10 mL). The tetrahydrofuran is removed under reduced pressure and the aqueous layer is extracted with methylene chloride (5 X 30 mL). The combined organic layers are washed with water (10 mL), dried (sodium sulfate), concentrated and the residue is purified by gravity column chromatography (10 to 40 % ethyl acetate in hexane) to give 58 mg of the title product.

Physical characteristics are as follows:

¹H-NMR (CDCl₃) δ 0.76-1.01, 1.50-1.70, 2.05-2.30, 2.45, 2.76-2.96, 4.19-4.33, 5.95, 6.09, 7.00-7.48.

FAB-MS [M]⁺ = 362.

EXAMPLE 14 6-(1'-Ethyl-propyl)-4-hydroxy-3-(1'-phenyl-propyl)-2-pyrone; also named as 3-(.alpha.-ethylbenzyl)-1-ethylpropyl-4-hydroxy-2H-Pyran-2-one (Formula H-4: R₁ is ethyl; R₂ is ethyl) Refer to Chart H.

To a solution of 125 mg of H-3 and 56 mg of diisopropylamine in tetrahydrofuran (10 mL) is added 1.0 mL of 1.6 M n-butyl lithium-hexane solution at 0 °C and allowed to stir for 10 min. To the reaction is added 164 mg of iodoethane. The reaction mixture is stirred at 0 °C for 2 h, then is quenched with 2 N hydrochloric acid (2 mL) and water (10 mL). The tetrahydrofuran is removed under reduced pressure and the aqueous layer is extracted with methylene chloride (5 X 30 mL). The combined organic layers are washed with water (10 mL), dried (sodium sulfate), concentrated and the residue is purified by gravity column chromatography (10 to 40 % ethyl acetate in hexane) to give 89 mg of the title product.

Physical characteristics are as follows:

¹H-NMR (CDCl₃) δ 0.80, 0.93, 1.56, 2.06-2.21, 2.27, 4.23, 6.10, 7.14-7.49.

FAB-MS [M]⁺ = 300.

EXAMPLES 15-25

Following procedures analogous to those described above and using starting materials and reactants readily known and available to one of ordinary skill in organic synthesis, the following additional compounds of the present invention are prepared:

EXAMPLE 15 4-Hydroxy-6-(trans-4'-methoxybenzylidene)-methyl-3-(1'-phenylpropyl)-2-pyrone; also named as 3-(.alpha.-ethylbenzyl)-4-hydroxy-6-(p-methoxystyryl)-2H-Pyran-2-one

Physical characteristics are as follows:

$^1\text{H-NMR}$ (CD_3OD) δ 0.94, 2.27, 4.61, 5.97, 6.50, 6.62, 7.12-7.56.

FAB-MS $[\text{M}]^+ = 362$.

EXAMPLE 16 3-(.alpha.-ethylbenzyl)-4-hydroxy-6-(2-naphth-2-ylethyl)-2H-Pyran-2-one

5 Physical characteristics are as follows:

Mass Spectral Data (EI mode) Found: 384.1736.

EXAMPLE 17 3-(.alpha.-ethylbenzyl)-4-hydroxy-6-(1-ethyl-2-naphth-2-ylethyl)-2H-Pyran-2-one

Physical characteristics are as follows:

Mass Spectral Data (EI mode) Found: 412.2033.

10 EXAMPLE 18 3-(.alpha.-ethylbenzyl)-4-hydroxy-6-(2-naphth-1-ylethyl)-2H-Pyran-2-one

Physical characteristics are as follows:

Mass Spectral Data (EI mode) Found: 384.1736.

EXAMPLE 19 3-(.alpha.-ethylbenzyl)-4-hydroxy-6-(1-ethyl-2-naphth-1-ylethyl)-2H-Pyran-2-one

Physical characteristics are as follows:

15 Mass Spectral Data (EI mode) Found: 412.2041.

EXAMPLE 20 3-(.alpha.-cyclopropylbenzyl)-4-hydroxy-6-methyl-2H-Pyran-2-one

Physical characteristics are as follows:

Mass Spectral Data (EI mode) Found: 256.1116.

EXAMPLE 21 3-(.alpha.-cyclopropylbenzyl)-4-hydroxy-6-(3-phenylpropyl)-2H-Pyran-2-one

20 Physical characteristics are as follows:

Mass Spectral Data (EI mode) Found: 360 (low resolution only).

EXAMPLE 22 3-(.alpha.-cyclopropylbenzyl)-6-(1-ethyl propyl)-4-hydroxy-2H-Pyran-2-one

Physical characteristics are as follows:

Mass Spectral Data (EI mode) Found: 312.1725.

25 EXAMPLE 23 3-(.alpha.-cyclopropylbenzyl)-6-(.alpha.-benzylphenethyl)-4-hydroxy-2H-Pyran-2-one

Physical characteristics are as follows:

Mass Spectral Data (EI mode) Found: 436.2035.

EXAMPLE 24 3-(.alpha.-cyclopropylbenzyl)-4-hydroxy-6-phenethyl-2H-Pyran-2-one

30 Physical characteristics are as follows:

Mass Spectral Data (EI mode) Found: 346.1568.

EXAMPLE 25 3-(.alpha.-cyclopropylbenzyl)-6-(1-propylbutyl)-4-hydroxy-2H-Pyran-2-one

Physical characteristics are as follows:

Mass Spectral Data (EI mode) Found: 340.2042.

35 PREPARATION 12 Methyl 2-(.alpha.-ethylbenzyl)-acetoacetate (Formula I-3) Refer to Chart I.

To a stirred suspension of 216 mg of sodium hydride in 15 mL of dry tetrahydrofuran at

0 °C is added 0.86 mL of methylacetoacetate of formula I-1. After 15 min. a solution of 1.9 g of α -ethylbenzyl bromide of formula I-2 in 5 mL of tetrahydrofuran is added. The resulting reaction mixture is heated to 65 °C for 2 days. The cooled mixture is then partitioned between diethyl ether and 1N aqueous hydrochloric acid. The aqueous phase is extracted with two more portions of diethyl ether. The combined organic phase is dried over magnesium sulfate, and then concentrated. The resulting residue is chromatographed on silica gel with 40-50% diethyl ether in hexane to give 0.53 g of diastereomeric title product.

Physical characteristics are as follows:

$^1\text{H-NMR}$ δ 7.4-7.1, 3.9-3.8, 3.76, 3.38, 3.3-3.2, 2.3, 1.89, 1.8-1.5, 0.94-0.88, 0.77-0.67.

10 PREPARATION 13 Methyl 2-(α -ethylbenzyl)-5-hydroxy-3-oxo-5-phenyl-heptanoate
(Formula I-5) Refer to Chart I.

To a stirred suspension of 60 mg of sodium hydride in 5 mL of dry tetrahydrofuran at 0 °C is added a solution of 0.53 g of methyl 2-(α -ethylbenzyl)-acetoacetate of Preparation 12 in 5 mL of tetrahydrofuran. The resulting mixture is allowed to stir at room temperature for 1 hr, and then recooled to 0 °C. A solution of 1.55 mL of 1.6 M *n*-butyllithium in hexane is then slowly added. After 15 min, 0.33 mL of propiophenone of formula I-4 is added. After 30 min, 1 mL of concentrated aqueous hydrochloric acid is added, and the resulting mixture partitioned between water and diethyl ether. The aqueous phase is extracted with two more portions of diethyl ether. The combined organic phase is dried over magnesium sulfate, and then concentrated. The resulting residue was chromatographed on silica gel with 5-15% ethyl acetate in hexane to give 0.48 g of diastereomeric title product.

Physical characteristics are as follows:

$^1\text{H-NMR}$ consistent with mixture of tautomers and diastereomers of the title product;

MS-EI: M^+ -29=368, fragments consistent with structure.

25 EXAMPLE 26 6-Ethyl-3-(α -ethylbenzyl)-6-phenyl-tetrahydropyran-2,4-dione (Formula I-6)
Refer to Chart I.

To a stirred solution of 149 mg of methyl 2-(α -ethylbenzyl)-5-hydroxy-3-oxo-5-phenyl-heptanoate of Preparation 13 in 10 mL of tetrahydrofuran is added 40 mL of 0.1 N aqueous sodium hydroxide. After 4 hr, the reaction mixture is concentrated to remove tetrahydrofuran and the remaining aqueous phase is washed with two portions of diethyl ether. The aqueous phase is cooled to 0 °C, and then acidified with 2N aqueous hydrochloric acid. It is extracted with four portions of diethyl ether, and the combined organic phase dried over magnesium sulfate, and then concentrated. The residue is chromatographed on silica gel with 30% ethyl acetate in hexane to give 69 mg of tautomeric title product.

Physical characteristics are as follows:

$^1\text{H-NMR}$ δ 7.3-7.1, 4.0-3.9, 3.6-3.3, 3.1-2.9, 2.2-1.6, 0.9-0.5;

MS-EI: M^+ =336.1722 found.

PREPARATION 14 Methyl 2-(3-phenylpropyl)-acetoacetate (Formula J-3) Refer to Chart J.

To a stirred suspension of 240 mg of sodium hydride in 20 mL of dry tetrahydrofuran at 0 °C is added 0.9 mL of methylacetoacetate of formula J-1. After 30 min, a solution of 1.6 mL of 1-bromo-3-phenylpropane of formula J-2 in 5 mL of tetrahydrofuran is added. The resulting reaction mixture is heated to 65 °C overnight. The cooled mixture is then partitioned between diethyl ether and 1N aqueous hydrochloric acid. The aqueous phase is extracted with two more portions of diethyl ether. The combined organic phase is dried over magnesium sulfate, and then concentrated. The resulting residue is chromatographed on silica gel with 40% ethyl acetate in hexane to give 0.75 g of the title product.

Physical characteristics are as follows:

$^1\text{H-NMR}$ δ 7.3-7.1, 3.72, 3.44, 2.61, 2.19, 1.92-1.85, 1.67-1.26.

PREPARATION 15 Methyl 2-(3-phenylpropyl)-5-ethyl-5-hydroxy-3-oxo-heptanoate (Formula J-5) Refer to Chart J.

To a stirred suspension of 84 mg of sodium hydride in 8 mL of dry tetrahydrofuran at 0 °C is added a solution of 0.75 g of methyl 2-(3-phenylpropyl)-acetoacetate of Preparation 14 in 5 mL of tetrahydrofuran. The resulting mixture is allowed to stir at room temperature for 30 min, and then recooled to 0 °C. A solution of 2.2 mL of 1.6 M *n*-butyllithium in hexane is then slowly added. After 15 min, 0.37 mL of 3-pentanone of formula J-4 is added. After 30 min, 1 mL of concentrated aqueous hydrochloric acid is added, and the resulting mixture partitioned between water and diethyl ether. The aqueous phase is extracted with two more portions of diethyl ether. The combined organic phase is dried over magnesium sulfate, and then concentrated. The resulting residue is chromatographed on silica gel with 10-25% ethyl acetate in hexane to give 0.435 g of the title product.

Physical characteristics are as follows:

$^1\text{H-NMR}$ δ 7.3-7.1, 3.71, 3.5-3.4, 2.7-2.3, 1.9-1.8, 1.6-1.4, 0.86-0.81.

EXAMPLE 27 6,6-Diethyl-3-(3-phenylpropyl)-tetrahydropyran-2,4-dione (Formula J-6) Refer to Chart J.

To a stirred solution of 435 mg of methyl 2-(3-phenylpropyl)-5-ethyl-5-hydroxy-3-oxo-heptanoate of Preparation 15 in 20 mL of tetrahydrofuran is added 100 mL of 0.125 N aqueous sodium hydroxide. After 4 hr, the reaction mixture is concentrated to remove tetrahydrofuran and the remaining aqueous phase is washed with three portions of diethyl ether. The aqueous phase is cooled to 0 °C, and then acidified with 2N aqueous hydrochloric acid. It is extracted with four portions of diethyl ether, and the combined organic phase dried over magnesium sulfate, and then concentrated. The residue is chromatographed on silica gel with 40% ethyl acetate in hexane to give 316 mg of tautomeric title product.

-75-

Physical characteristics are as follows:

$^1\text{H-NMR}$ δ 9.34, 7.3-7.1, 3.22, 2.7-2.3, 2.14, 2.05, 1.8-1.6, 0.97-0.85;

MS-EI: M^+ =288.1734 found.

PREPARATION 16 GENERAL PROCEDURES FOR THE FOLLOWING PREPARATIONS
AND EXAMPLES

A. General Procedure for the Dianion Synthesis of 5,6-Dihydropyrone

Methyl acetoacetate is dissolved in tetrahydrofuran (0.5 M) at 0 °C. Sodium hydride (1.1 equivalent, 60% dispersion in mineral oil) is added and the reaction is stirred 15 minutes at 0 °C. Then *n*-butyl lithium (1.1 equivalents, 1.6 M solution in hexane) is added dropwise and the reaction is stirred 15 minutes at 0 °C. The ketone is dissolved in tetrahydrofuran, then added all at once to the reaction mixture. The reaction is stirred an additional hour, then poured into a saturated ammonium chloride solution. It is extracted with methylene chloride, dried over anhydrous sodium sulfate and evaporated in vacuo. The material obtained is dissolved in tetrahydrofuran (0.3 M) and a 0.1 N sodium hydroxide (1 eq.) solution is added. After stirring one hour, the mixture is extracted with ethyl acetate (1 X). The aqueous layer is adjusted to pH 3 with hydrochloric acid, then extracted with ethyl acetate, dried over anhydrous sodium sulfate and evaporated to afford the desired pyrone product.

B. General Procedure for the Palladium Catalyzed Allylic Alkylation

Pyrone or 5,6-dihydropyrone (1 eq.), methyl-(1-phenyl-3-trimethylsilyl)-2E-propenyl)carbonate (1.1 eq.), or other appropriately substituted carbonate, palladium acetate (0.05 equivalent) and triphenylphosphine (0.20 equivalents) are suspended in distilled toluene under a carefully flushed atmosphere of nitrogen. The reaction is heated to 70 °C for 1-2 hr. Then the reaction mixture is poured into water, extracted with ethyl acetate and purified by flash column chromatography on silica gel with ethyl acetate/hexane solvent mixture to afford the desired 3-substituted pyrones or 5,6-dihydropyrone.

C. General Procedure for Protodesilylation

The vinylsilane from B. (1 eq) and *p*-toluene sulfonic acid (0.5 eq) are refluxed in acetonitrile 1-2 hr. The reaction is poured into water, extracted with ethyl acetate, dried over anhydrous sodium sulfate, and evaporated in vacuo to provide the desilylated 3-substituted pyrone or 5,6-dihydropyrone product.

D. General Procedure for Catalytic Hydrogenation

The olefinic 3-substituted products from C. above are dissolved in methanol, ethanol or a mixture of methanol/tetrahydrofuran. 10% Palladium hydroxide or palladium on carbon is added and the mixture hydrogenated at 40 psi for 4-6 hr. Filtration, evaporation and either flash column chromatography or crystallization give the desired product.

EXAMPLE 28 Dimethyl 3-[(4-hydroxy-2-oxo-6-phenyl-2H-1-pyran-3-yl)(4-nitrophenyl)methyl]

-76-

-1,3-propandioate

4-Hydroxy-6-phenyl-2H-pyran-2-one (0.5 g), dimethyl (4-nitrobenzylidene) malonate (0.70 g) and cesium carbonate (0.86 g) are suspended in 7 mL of tetrahydrofuran and refluxed for 2 h. Then the reaction is cooled to room temperature, diluted with water and extracted with 5 methylene chloride. The organic layer is washed with brine, dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification by flash column chromatography (5% ethyl acetate/methylene chloride) affords 0.16 g of the desired title product as a mixture of diastereomers. (Some of the product may be lost in the aqueous layers, because they are not neutralized.)

10 Physical characteristics mixture of diastereomers are as follows:

^1H NMR(300 MHz, CD_3OD): δ 8.10, 7.63, 7.36, 5.31, 4.99, 3.69, 3.53, 2.86, 2.70.

HRMS Found: 456.1296.

EXAMPLE 29 Dimethyl 3-[(4-hydroxy-2-oxo-6-phenyl-2H-1-pyran-3-yl)(3-nitrophenyl)methyl]

-1,3-propandioate

15 Dimethyl (3-nitrobenzylidene)malonate (2.54 g), 1.83 g of 4-hydroxy-6-phenyl-2H-pyran-2-one, and cesium carbonate (3.44 g) are suspended in 24 mL of tetrahydrofuran and refluxed for 3 h. After cooling to room temperature, the reaction is poured into 2 N hydrochloric acid and extracted with ethyl acetate. The organic layers are washed with brine, dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification by flash column 20 chromatography (5% methanol/chloroform) affords 4.16 g of the title product as a mixture of diastereomers (foam).

Physical characteristics are as follows:

IR(nujol): 3541-3035(br), 1754, 1738, 1703, 1646, 1529 cm^{-1} .

25 ^1H NMR(300 MHz, CDCl_3): δ 8.11, 7.84, 7.63, 7.21-7.02, 5.11, 5.01, 4.87-4.74, 3.54, 3.54, 3.39, 3.37, 2.74-2.53.

HRMS Found: 456.1296.

PREPARATION 17 Methyl-(1-phenyl-3-trimethylsilyl-2E-propenyl) carbonate (Formula K-2(c)) Refer to Chart K.

30 *t*-Butyllithium (116.4 mL, 1.7 M in pentane) is added to 188.4 mL of dried tetrahydrofuran under nitrogen and cooled to -78°C . (2-Bromovinyl)trimethylsilane (15.18 mL) is added dropwise over 10 minutes. The reaction is stirred for 15 min at -78°C , then 10.00 g of benzaldehyde is added via syringe. The reaction is stirred at -78°C for 45 min. The reaction is quenched with freshly distilled methyl chloroformate (7.64 mL). The mixture is allowed to warm up to room temperature and the stirring is continued for 2 h at which time it is 35 poured into water and extracted with ethyl acetate, washed with brine, dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification by flash column chromatography (1%,

then 2% ethyl acetate:hexane) provides 21.5 g of an oil.

Physical characteristics are as follows:

^1H NMR (300MHz, CDCl_3): δ 7.33-7.18, 6.10, 5.99, 5.90, 3.71, 0.03.

HRMS Found: 264.1189.

- 5 PREPARATION 18 Methyl [1-(3-benzyloxyphenyl)-3-trimethylsilyl-2E-propenyl] carbonate
(Formula K-2(a) and K-2(b)) Refer to Chart K.

The title product is obtained by following the one-step procedure used for the synthesis of methyl (1-phenyl-3-trimethylsilyl-2E-propenyl) carbonate of Preparation 17 but substituting 3-benzyloxybenzaldehyde (6.58 g) for benzaldehyde.

- 10 Purification by flash column chromatography (5% ethyl acetate:hexane) provides 8.18 g of oil.

Physical characteristics are as follows:

^1H NMR (300 MHz, CDCl_3): δ 7.39-7.12, 6.92-6.85, 6.06, 5.96, 5.91, Hz 5.00, 3.71, 0.01.

- 15 MS m/e (rel %): 370(85), 279(13), 204(63), 203(69), 189(80), 91(100), 73(37).

PREPARATION 19 5,6-Dihydro-4-hydroxy-6-phenyl-6-propyl-2H-pyran-2-one (Formula K-1(a)) Refer to Chart K.

- Methylacetoacetate (8.0 g) is dissolved in 60 ml tetrahydrofuran and chilled to 0 °C. Sodium hydride (3.03 g of 60% dispersion in mineral oil) is added and the mixture is stirred for 20 15 minutes at 0 °C. *n*-Butyllithium (47.4 ml of 1.6 M in hexanes) is added dropwise. After 15 minutes, 11.5 ml of butyrophenone in 5 ml tetrahydrofuran is added at once. The reaction is stirred one hour at 0 °C, then poured into saturated ammonium sulfate solution and extracted with methylene chloride. The extract is dried over anhydrous sodium sulfate and evaporated in vacuo to an oil. The oil is dissolved in 180 ml tetrahydrofuran and 680 ml 0.1 N sodium 25 hydroxide solution is added. After 2 hr of stirring at room temperature, the mixture is extracted with ethyl acetate (1 X). The aqueous layer is adjusted to pH 3 with hydrochloric acid, then extracted with chloroform/methanol. The extract is dried over sodium sulfate and evaporated to give 12.54 g of white solid.

Physical characteristics are as follows:

- 30 Mp 130-132 °C

^1H NMR (300 MHz, CDCl_3): δ 7.40-7.25, 3.35, 3.23, 2.91, 2.88, 1.95, 1.33-1.25, 0.87.

IR (mineral oil mull): 1663, 1635, 1592, 1582, 1450 1342, 1332, 1319, 1285, 1263, 1244, cm^{-1} .

MS m/e (rel %): 232(2), 189(50), 149(11), 147(11), 105(100).

- 35 PREPARATION 20 5,6-Dihydro-4-hydroxy-6-phenyl-6-propyl-3-[1-(3-benzyloxyphenyl)-3-trimethylsilyl-2E-propenyl]-2H-pyran-2-one (Formula K-3(a)) Refer to

-78-

K.

4-hydroxy-6-phenyl-6-propyl-2H-pyran-2-one of Preparation 19 and starting material 10 (3.50 g, 10 mmol) and (E)-3-trimethylsilyl-2-propenyl carbonate of Preparation 18 (3.50 g, 10 mmol) in distilled toluene. Palladium acetate (96 mg) and triphenylphosphine (1.0 g, 3 mmol) are added. The mixture is topped with a condenser, carefully flushed with nitrogen and stirred at 80°C for 24 h. The mixture is poured into water, extracted with ethyl acetate, dried, and evaporated. Flash column chromatography on a silica gel column (10% ethyl acetate in hexane) affords 2.97 g of the title product as a mixture of diastereomers. The physical properties are as follows:

MR complicated by presence of diastereomers:

$^1\text{H NMR}$ (CDCl_3): δ 7.48-7.34, 6.92, 6.85-5.18, 5.11-4.87, 3.25-2.92, 1.98, 0.1.

$^{13}\text{C NMR}$ (CDCl_3): δ 164.7, 159.2, 158.6, 146.3, 142.8, 142.4, 142.2, 136.5, 134.4, 128.3, 127.8, 127.7, 127.5, 127.3, 124.8, 124.7, 120.2, 119.7, 118.8, 69.7, 69.5, 46.0, 45.2, 45.0, 37.1, 36.7, 16.5, 13.8, -1.5.
 IR (KBr): ν 3400 (broad), 1650, 1600, 1500, 1450, 1380, 1300, 1250, 1150, 1100, 1050, 1000, 950, 900, 850, 800, 750, 700, 650, 600, 550, 500, 450, 400, 350, 300, 250, 200, 150, 100, 50, 0.

4-hydroxy-6-phenyl-6-propyl-3-[1-(3-benzyloxyphenyl)-2-propenyl]-2H-pyran-2-one

4-hydroxy-6-phenyl-6-propyl-3-[1-(3-benzyloxyphenyl)-2-propenyl]-2H-pyran-2-one of Preparation 20 (2.95 g) is desilylated using the general procedure for the desilylation of silyl enol ethers to afford 2.53 g of the desired title product.

Physical properties are as follows:

$^1\text{H NMR}$ (CDCl_3): δ 7.34-7.15, 6.90-6.40, 6.35-5.80, 5.28-4.22, 3.10-2.78, 0.1.

MR complicated by presence of diastereomers.)

144.

4-hydroxy-6-phenyl-6-propyl-3-[1-(3-hydroxyphenyl)-propyl]-2H-pyran-2-one

4-hydroxy-6-phenyl-6-propyl-3-[1-(3-benzyloxyphenyl)-2-propenyl]-2H-pyran-2-one of Preparation 21 is hydrogenated using the general procedure for the hydrogenation of enol ethers to afford 1.88 g of the crude product. Flash column chromatography on silica gel (10% methylene chloride in hexane) affords 1.59 g of white solid (mixture of diastereomers). Recrystallizations from acetonitrile yield 450 mg of one diastereomer.

Physical properties of the crystalline diastereomer are as follows:

$^1\text{H NMR}$ (CD_3OD): δ 7.40, 7.00, 6.81, 6.62, 3.87, 3.16, 2.25-1.90, 1.51-1.20.

1.37, 1.30-1.15, 0.95, 0.73.

Analysis Found: C, 74.94; H, 7.38; N, 0.10.

MS m/e (rel %): 366(43), 348(7), 192(34), 175(78), 146(89), 118(100).

IR (mineral oil mull): 1645, 1616, 1599, 1588, 1495, 1448, 1321, 1252, 1225, 1160

5 cm^{-1} .

PREPARATION 22 5,6-Dihydro-4-hydroxy-6-cyclohexyl-6-phenyl-2H-pyran-2-one (Formula K-1(b)) Refer to Chart K.

Cyclohexylphenyl ketone (14.92 g) is converted to the title product using the general procedure for synthesis of 5,6-dihydropyrones of Preparation 16, A. to yield 15.34 g of a white solid of the title product.

Physical characteristics are as follows:

Mp 168-170 °C.

^1H NMR (300 MHz, CD_3OD): δ 7.48, 3.19, 2.05-1.75, 1.45-1.05.

15 ^{13}C NMR (75 MHz, d_6 -DMSO): δ 172.0, 166.4, 141.8, 127.9, 127.2, 125.5, 91.2, 85.1, 47.7, 33.5, 26.7, 26.5, 25.8.

MS m/e (rel %): 272(1), 189(62), 160(5), 147(12), 131(5), 105(100).

IR (mineral oil mull): 1675, 1629, 1598, 1474, 1447, 1349, 1297, 1280, 1265, 1255, 1240, 1215 cm^{-1} .

20 PREPARATION 23 5,6-Dihydro-4-hydroxy-6-cyclohexyl-6-phenyl-3-[1-(3-benzyloxyphenyl)-3-trimethylsilyl-2E-propenyl]-2H-pyran-2-one (Formula K-3(b)) Refer to Chart K.

5,6-Dihydro-4-hydroxy-6-cyclohexyl-6-phenyl-2H-pyran-2-one (2.48 g) of Preparation 22 is reacted with methyl [1-(3-benzyloxyphenyl)-3-trimethylsilyl-2E-propenyl] carbonate of Preparation 18 following the general palladium catalyzed alkylation procedure of Preparation 16, B. Flash column chromatography on silica gel with 25% ethyl acetate:hexane affords 2.63 g of the title product as an amorphous solid (mixture of diastereomers).

Physical characteristics are as follows:

Mp 89-91 °C.

30 ^1H NMR (300 MHz, CDCl_3): δ 7.50-7.35, 7.00-6.88, 6.50-5.69, 5.13-4.83, 3.31-2.89, 2.00-1.65, 1.42-0.90, 0.13 and 0.00. (^1H NMR complicated by presence of diastereomers.)

MS m/e (rel %): 566(5), 483(11), 393(5), 261(4), 213(8), 171(17), 129(7), 105(14), 91(100).

PREPARATION 24 5,6-Dihydro-4-hydroxy-6-cyclohexyl-6-phenyl-3-[1-(3-benzyloxyphenyl)-2E-propenyl]-2H-pyran-2-one

35 5,6-Dihydro-4-hydroxy-6-cyclohexyl-6-phenyl-3-[1-(3-benzyloxyphenyl)-3-trimethylsilyl-2E-propenyl]-2H-pyran-2-one of Preparation 23 (2.62 g) is desilylated using the general

-80-

procedure of Preparation 16, C. to provide 2.26 g of product.

Physical characteristics are as follows:

Mp 163-165 °C.

¹H NMR complicated by presence of diastereomers.

5 ¹H NMR (300 MHz, CDCl₃): δ 7.36-7.17, 6.84-6.78, 6.42-5.21, 4.98-4.77, 4.05-3.98, 3.15-2.75, 1.82-1.50, 1.19-0.78.

MS m/e (rel %): 494(5), 411(35), 291(10), 270(4), 224(5), 213(7), 171(15), 105(36), 91(100).

10 EXAMPLE 31 5,6-Dihydro-4-hydroxy-6-cyclohexyl-6-phenyl-3-[1-(3-hydroxyphenyl)propyl]-2H-pyran-2-one

5,6-Dihydro-4-hydroxy-6-cyclohexyl-6-phenyl-3-[1-(3-benzyloxyphenyl)-2E-propenyl]-2H-pyran-2-one (2.22 g) of Preparation 24 is hydrogenated using the general procedure of Preparation 16, D. Flash column chromatography on silica gel with 25-50% ethyl acetate:hexane yields 0.97 g of the title product as a foamy solid and a mixture of diastereomers.

15 Physical characteristics are as follows:

IR (mineral oil mull): 1645, 1616, 1599, 1588, 1448, 1334, 1260, 1255, 1235, 1160 cm⁻¹.

¹H NMR (300 MHz, d₆-DMSO): δ 9.01, 8.99, 7.32-7.20, 6.90-6.32, 3.83-3.45, 3.15-2.98, 1.95-1.50, 1.18-0.69, 0.209 and 0.20.

20 HRMS Found: 406.2144.

Anal. Found: C, 75.36; H, 7.58; N, 0.10.

PREPARATION 25 5,6-Dihydro-4-hydroxy-6-phenyl-6-propyl-3-(1-phenyl-3-trimethylsilyl-2E-propenyl)-2H-pyran-2-one

25 5,6-Dihydro-4-hydroxy-6-phenyl-6-propyl-2H-pyran-2-one (2.50 g) of Preparation 19 is treated with methyl (1-phenyl-3-trimethylsilyl-2E-propenyl) carbonate of Preparation 17, using the general procedure for palladium catalyzed alkylation of Preparation 16, B. to afford 6.50 g of crude product. Purification by flash column chromatography on silica gel (25% ethyl acetate:hexane) affords 2.68 g of the title product as a mixture of diastereomers.

Physical characteristics are as follows:

30 ¹H NMR (300 MHz, CDCl₃): δ 7.44-7.05, 6.74-5.62, 5.10-5.03, 3.18-2.93, 2.05-1.90, 1.52-1.20, 0.91 and 0.89, 0.10 and 0.00. (¹H NMR complicated by the presence of diastereomers.)

MS m/e (rel %): 420(6), 402(9), 377(22), 303(14), 287(25), 274(12), 230(13), 184(34), 173(55), 73(100).

35 EXAMPLE 32 5,6-Dihydro-4-hydroxy-6-phenyl-6-propyl-3-(1-phenylpropyl)-2H-pyran-2-one

A) 5,6-Dihydro-4-hydroxy-6-phenyl-6-propyl-3-(1-phenyl-3-trimethylsilyl-2E-

un-2-one (2.65 g) of Preparation 25 is desilylated using the general procedure C. to provide 2.21 g of the desired product, which is carried on to the next py further purification.

Characteristics are as follows:

(rel %): 348(18), 330(19), 305(37), 287(29), 277(17), 230(17), 184(28), 131(49), 117(100).

5,6-Dihydro-4-hydroxy-6-phenyl-6-propyl-3-(1-phenyl-2E-propenyl)-2H-pyran-2-one (3.26 g) is hydrogenated using the general procedure of Preparation 16, D. The product is purified from acetonitrile to give 947 mg of the desired title product. NMR of the major diastereomer had crystallized from the diastereomeric mixture.

Characteristics of one diastereomer is as follows:

mp: 98 °C.

(300 MHz, d_6 -DMSO): δ 7.35-7.23, 7.12-6.98, 3.72-3.68, 3.07, 2.05-1.65, 0.90, 0.77, 0.50.

(rel %): 350(5), 332(4), 306(42), 277(29), 173(91), 159(47), 146(52).

IR (oil mull): 1642, 1603, 1595, 1575, 1448, 1329, 1317, 1276 cm^{-1} .

Found: C, 78.50; H, 7.61.

26 4-Hydroxy-1-oxaspiro[5.5]undec-3-en-2-one (Formula K-1(c)) Refer to Chart K.

3,4-Dihydro-2H-pyran-2-one (3.89 g) is converted to the title product using the general procedure for the synthesis of 5,6-dihydropyran-2-ones of Preparation 16, A. Crystallization from diethyl ether provides the desired title product (3.26 g).

Characteristics are as follows:

mp: 120 °C.

(300 MHz, CDCl_3): δ 3.41, 2.67, 1.89-1.72, 1.60-1.32.

^{13}C (75 MHz, CDCl_3): δ 200.7, 167.3, 80.4, 49.4, 44.4, 36.8, 24.5, 21.4.

(rel %): 182(41), 139(28), 126(86), 111(11), 98(44), 84(100).

IR (oil mull): 1653, 1615, 1581, 1351, 1325, 1285, 1265, 1256, 1223, 1014 cm^{-1} .

Found: C, 66.24; H, 7.88, N, 0.17.

27 4-Hydroxy-1-oxa-8-[1-phenyl-3-trimethylsilyl-2E-

propenyl]spiro[5.5]undec-3-en-2-one (Formula K-3(c)) Refer to Chart K.

4-Hydroxy-1-oxaspiro[5.5]undec-3-en-2-one (1.06 g) is reacted with methyl (1-phenyl-3-propenyl) carbonate of Preparation 17, using the general procedure for the regioselective alkylation of Preparation 16, B. to afford 2.75 g of the crude title product. Purification by chromatography on silica gel with 5% methanol:toluene, followed by similar

chromatography with 20% ethyl acetate:hexane, provides 1.26 g of the desired title product.

Physical characteristics are as follows:

^1H NMR (300 MHz, CDCl_3): δ 7.30-7.13, 6.52, 6.43, 5.65, 5.00, 2.45, 1.99-1.82, 1.79-1.20, 0.00.

5 MS m/e (rel %): 370(6), 352(15), 280(23), 247(19), 231(18), 198(17), 184(14), 173(21), 157(25), 73(100).

IR (mineral oil mull): 1641, 1612, 1602, 1450, 1303, 1287, 1261, 1247 cm^{-1} .

PREPARATION 28 4-hydroxy-1-oxa-3-(1-phenyl-2-propenyl)spiro-[5,5]-undec-3-en-2-one

4-Hydroxy-1-oxa-8-[1-phenyl-3-trimethylsilyl-2E-propenyl]spiro[5,5]undec-3-en-2-one

10 (1.25 g) of Preparation 27 is desilylated using the general procedure. Flash column chromatography on silica gel with 25% ethyl acetate:hexane provides 660 mg of a foamy solid.

Physical characteristics are as follows:

HRMS Found: 298.1567.

15 IR (mineral oil mull): 1631, 1493, 1449, 1431, 1338, 1331, 1316, 1304, 1286, 1268, 1244, 1232 cm^{-1} .

EXAMPLE 33 4-Hydroxy-1-oxa-3-(1-phenylpropyl)spiro-[5,5]-undec-3-en-2-one, sodium salt

4-hydroxy-1-oxa-3-(1-phenyl-2-propenyl)spiro-[5,5]-undec-3-en-2-one (0.63 g) of

Preparation 28 is hydrogenated using the general procedure to provide 640 mg of product as an oil. The oil is dissolved in methanol and 0.487 ml of sodium methoxide (25% wt in methanol)

20 is added. The mixture is evaporated in vacuo and crystallized from acetonitrile to afford 375 mg of the title product.

Physical characteristics are as follows:

Mp 201-204 $^{\circ}\text{C}$.

25 ^1H NMR (300 MHz, CD_3OD): δ 7.55, 7.30, 7.16, 4.23, 2.52, 2.46-2.35, 2.23-2.02, 1.96-1.83, 1.78-1.50, 1.08.

^{13}C NMR (75 MHz, CD_3OD): δ 183.5, 172.8, 149.0, 129.1, 128.0, 125.2, 99.1, 77.7, 45.6, 42.5, 87.2, 37.0, 26.7, 26.2, 22.9, 13.5.

FAB MS $[\text{m}+\text{H}]^+$ at m/z 323.

IR (mineral oil mull): 1629, 1515, 1450, 1421, 1409, 1365, 1341, 1310 cm^{-1} .

30 Analysis Found: C, 68.60; H, 7.25.

EXAMPLE 34 Dihydro-6-methyl-6-phenyl-3-(1-phenyl-2-propenyl)-2H-Pyran-2,4(3H)-dione

Physical characteristics are as follows:

Mp 147-149 $^{\circ}\text{C}$.

EXAMPLE 35 Dihydro-3-(1-(3-hydroxyphenyl)propyl)-6-phenyl-6-propyl-2H-pyran-2,4(3H)-
35 dione

Physical characteristics of mixture of diastereomers are as follows:

MS m/e (relative intensity): 366(100), 192 (34), 175 (78), 146 (89).

PREPARATION 29 4-Hydroxy-6-phenethyl-2H-pyran-2-one (Formula M-2) Refer to Chart M.

To a flame-dried flask containing a stirred solution of 0.90 mL of diisopropylamine in 6 mL of anhydrous tetrahydrofuran at -78°C under an argon atmosphere is added 4.0 mL of a 1.6 M solution of n-butyllithium in hexane. The resulting solution is allowed to warm to 0°C for 20 min, and is then treated via cannula with a solution of 378 mg of commercially available 4-hydroxy-6-methyl-2-pyrone of formula M-1 in 15 mL of tetrahydrofuran. The resulting red, thick slurry is slowly treated with 6.0 mL of distilled hexamethylphosphoramide and allowed to stir for 30 min. The red, cloudy solution is then treated with 0.36 mL of benzyl bromide. The reaction quickly becomes a deep orange solution and is allowed to stir at 0°C for an additional 60 min. The mixture is quenched with excess 1 N aqueous hydrochloric acid and the resulting yellow, biphasic mixture is concentrated to remove the tetrahydrofuran. The resulting mixture is partitioned between dichloromethane and water and the acidic aqueous phase is further extracted with additional portions of dichloromethane. The combined organic phases is dried over magnesium sulfate and then concentrated under reduced pressure. The resulting material is diluted with a large volume of diethyl ether and washed with dilute aqueous hydrochloric acid. The ethereal phase is washed with two additional portions of hydrochloric acid, once with brine, dried over magnesium sulfate, and finally concentrated under reduced pressure. The residue is flash column chromatographed on silica gel 60 (230-400 mesh) eluting with 1% acetic acid and 20% to 40% ethyl acetate in dichloromethane to give 440 mg of the title compound as a tan solid.

Physical characteristics are as follows:

^1H NMR δ 2.7, 3.0, 5.46, 5.84, 7.1-7.3.

TLC R_f 0.38 (1% acetic acid and 25% ethyl acetate in dichloromethane.)

Mp 137-138 °C.

PREPARATION 30 6-(α -ethyl-phenethyl)-4-hydroxy-2H-pyran-2-one (Formula M-3) Refer to Chart M.

To a cold (-78°C) stirred solution of 0.29 ml of diisopropylamine in 4 ml of dry tetrahydrofuran, under argon, is added 1.2 ml of a 1.6 M solution of n-butyllithium in hexane. The solution is warmed to 0°C, kept at that temperature for ten minutes, then cooled to -30°C. Into this solution is cannulated a solution of 189 mg of compound of Preparation 29 in 4 ml of tetrahydrofuran. The resulting heterogeneous mixture is warmed to 0°, and sufficient hexamethylphosphoramide (ca 1 ml) is added to render the mixture mostly homogeneous. After the mixture is stirred for 30 minutes at 0°C, 77 μL of ethyl iodide is added dropwise. After another 90 minutes, the reaction is quenched with excess 1N hydrochloric acid, and

tetrahydrofuran is removed under reduced pressure. The residue is extracted with three portions of ethyl acetate, and the combined organic extract washed with dilute hydrochloric acid, dried (magnesium sulfate), and concentrated under reduced pressure. The residue is flash chromatographed on silica gel 60 (230-400 mesh) using 1% acetic acid and 25% ethyl acetate in dichloromethane to provide 182 mg of the title compound.

Physical characteristics are as follows:

^1H NMR δ 0.85, 1.6, 2.6, 2.9, 5.59, 5.86, 7.0-7.3.

FAB MS $[m+H]=245.1185$.

TLC R_f 0.33 (1% acetic acid and 25% ethyl acetate in dichloromethane.)

10 EXAMPLE 36 3-(α -Cyclopropyl-*meta*-(benzyloxycarbonylamino)benzyl)-6-(α -ethyl-phenethyl)-4-hydroxy-2H-pyran-2-one (Formula M-4) Refer to Chart M.

A mixture of 181 mg of the title compound of Preparation 30, 220 mg of the title compound of Preparation 37 (vide infra), 28 mg of p-toluenesulfonic acid monohydrate, and 600 mg of 3Å molecular sieves in 2 ml of benzene is refluxed under argon for 21 hours, then cooled and filtered through Celite. The filtrate is concentrated under reduced pressure, and the residue flash chromatographed on silica gel 60 (230-400 mesh) using 50-100% ethyl acetate in hexane to provide 250 mg of a mixture of materials. This is re-subjected to silica gel chromatography, using 5-20% ethyl acetate in dichloromethane, to afford 154 mg (40%) of the title compound.

Physical characteristics are as follows:

20 ^1H NMR δ 0.26, 0.48, 0.67, 0.81, 1.6, 1.8, 2.5, 2.7, 2.9, 3.48, 5.14, 5.86, 6.81, 7.0-7.5, 9.46.

EI HRMS $m/z=523.2350$.

TLC R_f 0.27 (5% ethyl acetate in dichloromethane.)

25 PREPARATION 31 3-(α -Cyclopropyl-*meta*-aminobenzyl)-6-(α -ethyl-phenethyl)-4-hydroxy-2H-pyran-2-one (Formula M-5) Refer to Chart M.

A mixture of 146 mg of the title compound of Example 36 and 50 mg of 5% palladium on carbon in 2 ml of methanol is shaken under 40 psi of hydrogen for two hours, then filtered through Celite. The filtrate is concentrated under reduced pressure to give 105 mg (96%) of the title compound.

30 Physical characteristics are as follows:

^1H NMR δ 0.25, 0.5, 0.65, 0.81, 1.6, 2.5, 2.7, 2.9, 3.4, 5.79, 6.5, 6.8-7.3.

TLC R_f 0.38 (30% ethyl acetate in dichloromethane).

35 EXAMPLE 37 N-(3-(Cyclopropyl-[6-(1-ethyl-phenethyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl)-phenyl)-3-(*tert*-butoxycarbonylamino)-propionamide (Formula M-6)
Refer to Chart M.

To a stirred solution of 50 mg of the title compound of Preparation 31 and 29 mg of

tert-butyloxycarbonyl- β -alanine in 0.5 ml of dichloromethane is added 22 μ L of diisopropylcarbodiimide. The solution is stirred for 18 hours, then flash chromatographed on silica gel 60 (230-400 mesh) using 5-10% methanol and 30% ethyl acetate in dichloromethane. Obtained is 71 mg of product contaminated by byproducts of the coupling reaction. The material is re-chromatographed on silica using 30-70% ethyl acetate in dichloromethane to afford 34 mg (47%) of the title compound as a white solid.

Physical characteristics are as follows:

^1H NMR δ 0.2, 0.5, 0.6, 0.81, 1.41, 1.6, 1.8, 2.4, 2.8, 2.9, 3.3, 3.4, 5.4, 5.8, 7.0-7.3, 7.5.

FAB HRMS $[m+H]=561.2995$.

TLC R_f 0.17 (30% ethyl acetate in dichloromethane.)

PREPARATION 32 6-(α -Cyclopropylmethyl-cyclopropylethyl)-4-hydroxy-2H-pyran-2-one
(Formula N-2) Refer to Chart N.

To a cold (-78°C) stirred solution of 1.5 ml of diisopropylamine in 9 ml of dry tetrahydrofuran, under argon, is added 6.2 ml of a 1.6 M solution of *n*-butyllithium in hexane. The solution is warmed to 0°C, and into it is cannulated a solution of 378 mg of commercially available 4-hydroxy-6-methyl-2-pyrone of formula N-1 in 8 ml of hexamethylphosphoramide. After 30 minutes at 0°C, 0.32 ml of bromomethylcyclopropane is added; after another ten minutes, a second portion of the same amount is added. The reaction is stirred and allowed to warm to room temperature overnight, then is partitioned between ethyl acetate and excess dilute hydrochloric acid. The organic phase is washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue is flash chromatographed on silica gel 60 (230-400 mesh) using 1% acetic acid and 25% ethyl acetate in dichloromethane to provide 371 mg of the title compound, along with 206 mg of monoalkylated material.

Physical characteristics are as follows.

^1H NMR δ 0.0, 0.4, 0.6, 1.5, 1.6, 2.2, 5.6, 6.1, 7.2-7.3, 11.5.

EI MS $m/z=234$.

TLC R_f 0.29 (1% acetic acid and 25% ethyl acetate in dichloromethane.)

EXAMPLE 38 3-(α -Cyclopropyl-*meta*-(*tert*-butyloxycarbonylamino)benzyl)-6-(α -cyclopropylmethyl-cyclopropylethyl)-4-hydroxy-2H-pyran-2-one (Formula N-3)
Refer to Chart N.

A mixture of 367 mg of the title compound of Preparation 32, 470 mg of the title compound of Preparation 37 (vide infra), 60 mg of *p*-toluenesulfonic acid monohydrate, and 1 g of 3 Å sieves in 5 ml of benzene is heated with stirring overnight under argon. The mixture is diluted with dichloromethane and ether and filtered through a pad of sodium sulfate. After the solvent is removed under reduced pressure, the residue is flash chromatographed on silica gel 60 (230-400 mesh) using 5-20% ethyl acetate in dichloromethane to afford 399 mg of the title

compound.

Physical characteristics are as follows:

^1H NMR δ -0.06, 0.3, 0.5, 1.4, 1.5, 2.5, 3.5, 5.1, 7.2-7.4.

EI HRMS m/z =513.2513.

5 TLC R_f 0.28 (5% ethyl acetate in dichloromethane.)

PREPARATION 33 3-(α -Cyclopropyl-*meta*-aminobenzyl)-6-(α -cyclopropylmethyl-
cyclopropylethyl)-4-hydroxy-2H-pyran-2-one (Formula N-4) Refer to
Chart N.

10 A mixture of 391 mg of the title compound of Example 38 and 100 mg of 5%
palladium on carbon in 10 ml of methanol is shaken overnight under 40 psi of hydrogen. The
mixture is then filtered through Celite, and the filtrate is concentrated under reduced pressure to
provide 280 mg of the title compound.

Physical characteristics are as follows:

^1H NMR δ 0.0, 0.2-0.7, 1.4, 1.6, 1.8, 2.6, 6.8, 7.2-7.4.

15 TLC R_f 0.38 (30% ethyl acetate in dichloromethane.)

EXAMPLE 39 N-(3-(Cyclopropyl-[6-(2-cyclopropyl-1-cyclopropylmethyl-ethyl)-4-hydroxy-2-
oxo-2H-pyran-3-yl]-methyl)-phenyl)-3-indol-1-yl-propionamide (Formula N-5)
Refer to Chart N.

20 A stirred solution of 50 mg of the title compound of Preparation 33 and 27 mg of 3-(1-
indolyl)-propionic acid in 1 ml of dichloromethane and 0.1 ml of dimethylformamide is cooled to
0°C, and to this is added 23 μL of diisopropylcarbodiimide. The solution is allowed to warm
slowly overnight, and the following day solvent is removed under reduced pressure. The residue
is flash chromatographed on silica gel 60 (230-400 mesh) using 0-4% methanol and 20% ethyl
acetate in dichloromethane to afford 24 mg of the title compound as a white solid.

25 Physical characteristics are as follows:

^1H NMR δ -0.06, 0.2-0.7, 1.4, 1.5, 2.6, 3.5, 4.4, 6.06, 6.41, 7.0-7.7, 7.80.

TLC R_f 0.41 (20% ethyl acetate in dichloromethane.)

PREPARATION 34 Cyclopropyl *meta*-nitrophenyl ketone (Formula O-2) Refer to Chart O.

30 A 250 ml three necked flask fitted with thermometer and addition funnel is charged with
130 ml of fuming 90% nitric acid. This is cooled to -10°C in a -40°C acetone bath, and into
the stirred liquid is added dropwise 21 ml of commercially available cyclopropyl phenyl ketone
of formula O-1. The rate of addition is regulated to maintain the reaction temperature at about
-10°C. The completed clear yellow solution is stirred for another 10 minutes at -10°C, then
poured into 1 L of crushed ice. The precipitated gummy yellow solid is extracted with 700 ml
35 of toluene, and the extract is washed twice with 5% sodium hydroxide solution and once with
brine, and dried over magnesium sulfate. After the solvent was removed under reduced

pressure, the residue was recrystallized from methanol at -25°C to give 14.6 g of the title compound as dense, pale yellow prisms. The mother liquor contained substantial amounts of the *ortho* isomer.

Physical characteristics are as follows:

5 ^1H NMR δ 1.2, 1.3, 2.7, 7.70, 8.3, 8.4, 8.85.

IR 1664, 1529, 1352, 1225, 1082, 1017, 852, 689 cm^{-1} .

Anal. Found: C, 62.89; H, 4.73; N, 7.32.

EI MS m/z 191.

TLC R_f 0.32 (25% ethyl acetate in hexane.)

10 PREPARATION 35 *meta*-Aminophenyl cyclopropyl ketone (Formula O-3) Refer to Chart O.

A solution of 5.76 g of the title compound of Preparation 34 is prepared with the aid of heat in 100 ml of methanol. To this is added 450 mg of 5% platinum on carbon catalyst, and the mixture is stirred vigorously under 1 atmosphere of hydrogen. After 5 hours, the mixture is filtered through a pad of Celite and the filtrate concentrated under reduced pressure to afford

15 4.89 g of the title compound as a greenish oil.

Physical characteristics are as follows:

^1H NMR δ 1.0, 1.2, 2.6, 3.9, 6.8, 7.2, 7.4.

TLC R_f 0.50 (80% ethyl acetate in hexane.)

20 PREPARATION 36 *meta*-Benzyloxycarbonylaminophenyl cyclopropyl ketone (Formula O-4)
Refer to Chart O.

To a cold (0°C), stirred solution of 4.89 g of the title compound of Preparation 35 and 6.3 ml of diisopropylethylamine in 90 ml of dichloromethane is added dropwise 4.7 ml of benzyl chloroformate, and the completed solution is allowed to warm to room temperature. After 4 hours, the mixture is washed with dilute hydrochloric acid, and the aqueous phase
25 extracted with two additional portions of dichloromethane. The combined organic phase is dried over magnesium sulfate and concentrated under reduced pressure to a yellow solid. This is triturated with two 30 ml portions of hexane, these being discarded, and the remaining solid is dried under vacuum to afford 8.74 g of the title compound.

Physical characteristics are as follows:

30 TLC R_f 0.45 (5% ethyl acetate in dichloromethane.)

PREPARATION 37 *meta*-Benzyloxycarbonylaminophenyl cyclopropyl carbinol (Formula O-5) Refer to Chart O.

To a stirred solution of 8.74 g of compound O-4 in 100 ml of tetrahydrofuran and 100 ml of ethanol is added, in portions, 4.5 g of sodium borohydride. After 3 hours at room
35 temperature, the mixture is cooled in ice for the addition of 100 ml of 1N hydrochloric acid. The mixture is thrice extracted with dichloromethane, and the combined extract dried over

magnesium sulfate. Solvent is removed under reduced pressure, and the residue flash chromatographed on silica gel 60 (230-400 mesh) using 40% ethyl acetate in hexane to provide 8.48 g of the title compound as a white crystalline solid. This is optionally recrystallized from ethyl acetate-hexane.

- 5 Physical characteristics are as follows:
 ^1H NMR δ 0.3-0.6, 1.1, 2.35, 3.92, 5.17, 7.1, 7.2-7.4.
 IR 1693, 1599, 1559, 1449, 1235, 1054, 697 cm^{-1} .
 Anal. Found: C, 72.57; H, 6.51; N, 4.61.

EXAMPLES 40-76

- 10 Following procedures analogous to those described above and using starting materials and reagents readily known and available to one of ordinary skill in the art of organic synthesis, the following additional compounds of the present invention are prepared:

EXAMPLE 40 4-Hydroxy-3-(1-phenyl-propyl)-6-(1-propyl-butyl)-pyran-2-one

Physical characteristics are as follows:

- 15 Melting point: 132-134 $^{\circ}\text{C}$.

EXAMPLE 41 4-Hydroxy-3-(1-phenyl-allyl)-6-(1-propyl-butyl)-pyran-2-one

Physical characteristics are as follows:

Melting point: 114-116 $^{\circ}\text{C}$.

EXAMPLE 42 3-(5-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-oxo-6H-pyran-2-yl)-propionic

- 20 acid tert-butyl ester

Physical characteristics are as follows:

Anal. Found: C, 71.16; H, 7.19.

EXAMPLE 43 3-(Cyclopropyl-phenyl-methyl)-6-(2-(3,5-dimethyl-isoxazol-4-yl)-ethyl)-4-

hydroxy-pyran-2-one

- 25 Physical characteristics are as follows:

Anal. Found: C, 71.07; H, 6.17; N, 4.28.

EXAMPLE 44 6-(2-(5-Tert-butyl-(1,2,4)oxadiazol-3-yl)-ethyl)-3-(cyclopropyl-phenyl-methyl)-4-

hydroxy-pyran-2-one

Physical characteristics are as follows:

- 30 Anal. Found: C, 70.26; H, 6.68, N, 6.10.

HRMS Found: 394.1896.

EXAMPLE 45 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(1-(tetrahydro-furan-3-ylmethyl)-

propyl)-pyran-2-one

Physical characteristics are as follows:

- 35 Anal. Found: C, 74.51; H, 7.63

HRMS Found: 368.1981.

EXAMPLE 46 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(2-phenyl-1-pyridin-2-ylmethyl-ethyl)-pyran-2-one

Physical characteristics are as follows:

HRMS Found: 437.1989.

5 EXAMPLE 47 3-(Cyclopropyl-phenyl-methyl)-6-(2-(1,3)dioxolan-2-yl-ethyl)-4-hydroxy-pyran-2-one

Physical characteristics are as follows:

HRMS Found: 342.1462.

10 EXAMPLE 48 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(4-morpholin-4-yl-butyl)-pyran-2-one

Physical characteristics are as follows:

HRMS Found: 383.2108.

EXAMPLE 49 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(2-pyridin-2-yl-ethyl)-pyran-2-one

Physical characteristics are as follows:

15 HRMS Found: 347.1531.

EXAMPLE 50 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(2-(2-methyl-thiazol-4-yl)-ethyl)-pyran-2-one

Physical characteristics are as follows:

HRMS Found: 367.1247.

20 EXAMPLE 51 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(2-quinolin-2-yl-ethyl)-pyran-2-one

Physical characteristics are as follows:

HRMS Found: 397.1688.

EXAMPLE 52 6-(1-(5-Chloro-thiophen-2-ylmethyl)-propyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one

25 Physical characteristics are as follows:

HRMS Found: 414.1042.

EXAMPLE 53 6-(3-Chloro-propyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one

Physical characteristics are as follows:

Anal. Found: C, 67.61; H, 5.89.

30 EXAMPLE 54 3-(Cyclopropyl-phenyl-methyl)-6-(1-(3,5-dimethyl-isoxazol-4-ylmethyl)-propyl)-4-hydroxy-pyran-2-one

Physical characteristics are as follows:

HRMS Found: 393.1932.

35 EXAMPLE 55 6-(1-(2-(4-Chloro-phenyl)-thiazol-4-ylmethyl)-propyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one

Physical characteristics are as follows:

Anal. Found: C, 68.25; H, 5.58; N, 2.52.

EXAMPLE 56 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(1-(tetrahydro-furan-2-ylmethyl)-propyl)-pyran-2-one

Physical characteristics are as follows:

5 HRMS Found: 368.1984.

EXAMPLE 57 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(1-thiophen-2-ylmethyl-propyl)-pyran-2-one

Physical characteristics are as follows:

Anal. Found: C, 72.33; H, 6.32.

10 EXAMPLE 58 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(1-tetrahydro-pyran-4-ylmethyl)-propyl)-pyran-2-one

Physical characteristics are as follows:

HRMS Found: 382.2142.

EXAMPLE 59 3-(Cyclopropyl-phenyl-methyl)-6-(1-furan-2-ylmethyl-propyl)-4-hydroxy-pyran-2-one

15

Physical characteristics are as follows:

HRMS Found: 364.1673.

EXAMPLE 60 3-(Cyclopropyl-phenyl-methyl)-6-(1-(1,3)dioxolan-2-ylmethyl-propyl)-4-hydroxy-pyran-2-one

20

Physical characteristics are as follows:

HRMS Found: 370.1775.

EXAMPLE 61 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(1-(tetrahydro-pyran-3-ylmethyl)-propyl)-pyran-2-one

Physical characteristics are as follows:

25 HRMS Found: 382.2140.

EXAMPLE 62 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(1-(tetrahydro-pyran-2-ylmethyl)-propyl)-pyran-2-one

Physical characteristics are as follows:

HRMS Found: 382.2141.

30 EXAMPLE 63 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(1-pyridin-2-ylmethyl-propyl)-pyran-2-one

Physical characteristics are as follows:

HRMS Found: 375.1837.

EXAMPLE 64 6-(4-Chloro-1-ethyl-butyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one

35

Physical characteristics are as follows:

Anal. Found: C, 69.65; H, 7.02; N, 8.26.

HRMS Found: 360.1492.

EXAMPLE 65 3-(Cyclopropyl-phenyl-methyl)-6-(3-(1,3)dioxan-2-yl-1-ethyl-propyl)-4-hydroxy-pyran-2-one

Physical characteristics are as follows:

5 HRMS Found: 398.2094.

EXAMPLE 66 6-(3-Chloro-1-ethyl-propyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one

Physical characteristics are as follows:

HRMS Found: 346.1332.

10 EXAMPLE 67 3-(Cyclopropyl-phenyl-methyl)-6-[ethyl-3-(tetrahydro-pyran-2-yloxy)-propyl]-4-hydroxy-pyran-2-one

Physical characteristics are as follows:

HRMS Found: 412.2237.

EXAMPLE 68 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(1-pyridin-4-ylmethyl-propyl)-pyran-2-one

15

Physical characteristics are as follows:

HRMS Found: 375.1829.

EXAMPLE 69 3-(Cyclopropyl-phenyl-methyl)-6-(1-ethyl-3-morpholin-4-yl-3-oxo-propyl)-4-hydroxy-pyran-2-one

20

Physical characteristics are as follows:

HRMS Found: 411.2057.

EXAMPLE 70 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(1-pyridin-3-ylmethyl-propyl)-pyran-2-one

Physical characteristics are as follows:

25 HRMS Found: 375.1827.

EXAMPLE 71 3-(Cyclopropyl-phenyl-methyl)-6-(1-ethyl-3-thiophen-3-yl-propyl)-4-hydroxy-pyran-2-one

Physical characteristics are as follows:

HRMS Found: 394.1593.

30 EXAMPLE 72 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-[1-(tetrahydro-pyran-3-ylmethyl)-butyl]-pyran-2-one

Physical characteristics are as follows:

HRMS Found: 396.2298.

EXAMPLE 73 3-(Cyclopropyl-phenyl-methyl)-6-(1-ethyl-4-morpholin-4-yl-butyl)-4-hydroxy-pyran-2-one

35

Physical characteristics are as follows:

HRMS Found: 41.2404.

EXAMPLE 74 3-(Cyclopropyl-phenyl-methyl)-6-[1-(2,3-dihydro-benzo[1,4]dioxin-2-ylmethyl)-propyl]-4-hydroxy-pyran-2-one

Physical characteristics are as follows:

5 HRMS Found: 432.1931.

EXAMPLE 75 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-isobutyl-pyran-2-one

Physical characteristics are as follows:

HRMS Found: 298.1566.

EXAMPLE 76 3-(Cyclopropyl-phenyl-methyl)-6-[1-(5,6-dihydro-2H-pyran-3-ylmethyl)-propyl]-4-hydroxy-pyran-2-one

10

Physical characteristics are as follows:

HRMS Found: 380.1987.

PREPARATION 38 5-Bromo-4-hydroxy-6-methyl-3-(1-phenyl-propyl)-pyran-2-one (Formula P-2) Refer to Chart P.

15 To a flask containing a suspension of 110 mg of 5-bromo-4-hydroxy-6-methyl-pyran-2-one of formula P-1 (preparation of this material is described in *Syn. Comm.* 1984, 14, 521) and 30 mg of *p*-toluenesulfonic acid hydrate in 10 mL of benzene is added 0.25 mL of commercial 1-phenyl-1-propanol. The flask is equipped with an addition funnel containing 3 Å molecular sieves (pre-wet with benzene) and a reflux condenser under an argon balloon. The mixture is placed in an 100°C oil bath. After 12 h, the resulting solution is cooled to room temperature and partitioned between diethyl ether and excess 1 N aqueous sodium hydroxide. The basic aqueous phase is washed with diethyl ether, acidified to pH1 with 6 N aqueous hydrochloric acid and the resulting precipitant repeatedly extracted chloroform-methanol. The combined organic layers are washed with brine, dried (magnesium sulfate), and concentrated under reduced pressure. The residue is purified by flash column chromatography on silica gel eluting with 100% ethyl acetate to 20% methanol in ethyl acetate to afford 123 mg of the title product as a white solid.

20

25

Physical characteristics are as follows:

¹H NMR δ 7.42, 7.22, 7.12, 4.20, 2.32, 2.28, 2.09, 0.90;

30 EI-MS: [M⁺]=322.0216 found

EXAMPLE 77 5-Bromo-6-(2-cyclopropyl-cyclopropylmethyl-ethyl)-4-hydroxy-3-(1-phenyl-propyl)-pyran-2-one (Formula P-3) Refer to Chart P.

To a flame-dried flask under an argon atmosphere is added 0.23 mL of distilled diisopropylamine and 1.6 mL of dry tetrahydrofuran. The solution is cooled to -78°C and treated with 1.0 mL (1.6 M in hexane) of *n*-butyllithium. The solution is warmed to 0°C for 15 min, then cooled to -30°C. The lithium diisopropylamine solution is treated with 162 mg of 5-

35

bromo-4-hydroxy-6-methyl-3-(1-phenyl-propyl)-pyran-2-one (the title product of Preparation 38) as a solution in 2.5 mL of tetrahydrofuran. The resulting orange-red solution is stirred for 30 min as the bath temperature rises to -20°C. The solution is then treated with 0.11 mL of commercial (bromomethyl)cyclopropane. The reaction mixture is allowed to warm to 0°C over 3 h. The reaction is then quenched with excess 1 N aqueous hydrochloric acid and partitioned between ethyl acetate and water. The aqueous phase is extracted with ethyl acetate and the combined organic layers are dried (magnesium sulfate) and then concentrated under reduced pressure. The residue is purified by flash column chromatography on silica gel eluting with 2% to 10% ethyl acetate in dichloromethane to afford 98 mg of the title product as a tan oil.

Physical characteristics are as follows:

^1H NMR δ 7.45, 7.3-7.1, 6.34, 4.24, 3.31, 2.3-2.1, 1.6-1.2, 0.91, 0.55, 0.35, 0.4-0.1;

EI-MS: $[\text{M}^+]=430.1134$ found.

PREPARATION 39 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-5-[2-(2-methoxy-ethoxy)-ethyl]-6-methyl-pyran-2-one (Formula Q-2) Refer to Chart Q.

To a flame-dried flask under an argon atmosphere is added 0.60 mL of distilled diisopropylamine and 4.0 mL of dry tetrahydrofuran. The solution is cooled to -78°C and treated with 2.7 mL (1.6 M in hexane) of *n*-butyllithium. The solution is warmed to 0°C for 20 min, then cooled to -40°C. The lithium diisopropylamine solution is treated with 513 mg of 3-(cyclopropyl-phenyl-methyl)-4-hydroxy-6-methyl-pyran-2-one of formula Q-1 (prepared as described in Example 20) as a solution in 17 mL of tetrahydrofuran. The orange dianion is formed over 20 min as the bath temperature rises to -20°C. The solution is then treated with 565 mg of 2-(2-methoxy-ethoxy)-ethyl tosylate as a solution in 2 mL of tetrahydrofuran. The reaction mixture is allowed to slowly warm to 0°C over 2 h. The reaction is quenched with excess 1 N aqueous hydrochloric acid and concentrated under reduced pressure. The residue is partitioned between ethyl acetate and water. The aqueous phase is extracted with additional portions of ethyl acetate. The combined organic layers are dried (magnesium sulfate) and then concentrated under reduced pressure. The residue is purified by flash column chromatography on silica gel eluting with 50% to 100% ethyl acetate in hexane to afford 105 mg the title product as a tan oil.

Physical characteristics are as follows:

^1H NMR δ 8.75, 7.50, 7.26, 7.17, 3.68, 3.48, 3.33, 2.66, 2.20, 2.0-1.8, 0.68, 0.50, 0.28;

EI-MS: $[\text{M}^+]=358.1777$ found.

EXAMPLE 78 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-5-[2-(2-methoxy-ethoxy)-ethyl]-6-propyl-pyran-2-one (Formula Q-3) Refer to Chart Q.

To a flame-dried flask under an argon atmosphere is added 0.125 mL of distilled diisopropylamine and 1.0 mL of dry tetrahydrofuran. The solution is cooled to -78°C and

-94-

treated with 0.55 mL (1.6 M in hexane) of *n*-butyllithium. The solution is warmed to 0°C for 15 min, then cooled to -30°C. The lithium diisopropylamine solution is treated with 93 mg of 3-(cyclopropyl-phenyl-methyl)-4-hydroxy-5-[2-(2-methoxy-ethoxy)-ethyl]-6-methyl-pyran-2-one (the title product of Preparation 39) as a solution in 2.5 mL of tetrahydrofuran. The orange dianion is formed over 30 min as the bath temperature rises to -20°C. The solution is then treated with 55 µL of ethyl iodide. The reaction mixture is allowed to warm to 0°C over 2 h. The reaction is quenched with excess 1 N aqueous hydrochloric acid and partitioned between ethyl acetate and brine. The aqueous phase is extracted with additional portions of ethyl acetate. The combined organic layers are dried (magnesium sulfate) and then concentrated under reduced pressure. The residue is purified by flash column chromatography on silica gel eluting with 2% to 6% ethyl acetate in dichloromethane to afford 51 mg of the title product as a tan oil.

Physical characteristics are as follows:

¹H NMR δ 8.77, 7.54, 7.3-7.1, 3.67, 3.46, 3.31, 2.66, 2.43, 1.95, 1.66, 0.94, 0.67, 0.49, 0.26;

EI-MS: [M⁺]=386.2097 found.

PREPARATION 40 3-Benzyl-4-phenyl-but-2-enoic acid, *tert*-butyl ester (Formula R-2) Refer to Chart R.

To a flame-dried flask under an argon atmosphere is added 400 mg of sodium hydride (60% by weight in oil) and 5 mL of dry benzene. The grey suspension is cooled to 5°C and treated dropwise with 2.0 mL of the reagent *tert*-butyl P,P-dimethylphosphonoacetate to control reaction. After 10 min, the mixture is warmed to room temperature. After an additional 1 h, the tan cloudy solution is cooled to 5°C and treated with 2.1 g of commercial 1,3-diphenylacetone of formula R-1. After 10 min, the reaction mixture is allowed to warm to room temperature and stirred overnight. The resulting orange cloudy suspension is partitioned between diethyl ether and cold aqueous phosphate buffer. The aqueous phase is extracted with an additional portion of diethyl ether. The combined organic layers are washed with brine, dried (magnesium sulfate) and then concentrated under reduced pressure. The resulting residue is purified by flash column chromatography on silica gel eluting with 30% to 40% dichloromethane in hexane to afford 2.96 g of the title product as a clear, colorless oil.

Physical characteristics are as follows:

¹H NMR δ 7.4-7.1, 7.10, 5.69, 3.94, 3.29, 1.48;

EI-MS: [M⁺]=308.

PREPARATION 41 3-Benzyl-4-phenyl-butanoic acid, *tert*-butyl ester (Formula R-3) Refer to Chart R.

To a Parr bottle containing 200 mg of 5% platinum on carbon is added 2.81 g of *tert*-butyl 3-benzyl-4-phenyl-butenate (the title product of Preparation 40) as a solution in 30 mL of

- ethyl acetate. The mixture is hydrogenated under 50 psi of hydrogen gas overnight. The black suspension is filtered through a pad of Celite with ethyl acetate washings and the filtrate concentrated under reduced pressure. The residue is purified by flash column chromatography on silica gel eluting with 50% dichloromethane in hexane to afford 2.41 g of the title product as a white solid. An analytical sample is prepared by recrystallization from methanol.

Physical characteristics are as follows:

Mp 77-78.5°C;

^1H NMR δ 7.3-7.1, 2.60, 2.47, 2.13, 1.43;

Anal. Found: C, 81.16; H, 8.38.

- 10 PREPARATION 42 2-(1-Benzyl-2-phenyl-ethyl)-3,5-dioxo-hexanoic acid, *tert*-butyl ester
(Formula R-4) Refer to Chart R.

- To a flame-dried flask under an argon atmosphere is added 0.15 mL of distilled diisopropylamine and 1.0 mL of dry tetrahydrofuran. The solution is cooled to -78°C and treated with 0.65 mL (1.6 M in hexane) of *n*-butyllithium. The solution is warmed to 0°C for 15 10 min, then re-cooled to -78°C. The lithium diisopropylamine solution is treated with 282 mg of *tert*-butyl 3-benzyl-4-phenyl-butanoate (the title product of Preparation 41) as a solution in 2.5 mL of tetrahydrofuran via cannula. The resulting *tan* enolate is formed over 20 min. The enolate solution is then treated with 85 μL of distilled diketene. The reaction mixture immediately turns bright yellow and is allowed to warm to 0°C over 1 h. The reaction is 20 maintained at 0°C for 2 h and then quenched by addition to cold dilute 1 M aqueous potassium hydrogen sulfate. The mixture is extracted with three portions of diethyl ether. The combined organic layers are dried (magnesium sulfate) and then concentrated under reduced pressure. The residue is purified by flash column chromatography on silica gel eluting with 10% to 20% ethyl acetate in hexane to afford 126 mg of the tautomeric title compound as a *tan* oil.

- 25 Physical characteristics are as follows:

^1H NMR δ 7.3-7.1, 5.52, 3.20, 2.8-2.6, 2.03, 1.49;

EI-MS: $[\text{M}^+]=394$.

- PREPARATION 43 3-(1-Benzyl-2-phenyl-ethyl)-4-hydroxy-6-methyl-pyran-2-one (Formula R-5) Refer to Chart R.

- 30 To a flask containing 315 mg of tautomeric *tert*-butyl 2-(1-benzyl-2-phenyl-ethyl)-3,5-dioxo-hexanoate (title product of Preparation 42) is added 3 mL of trifluoroacetic acid. The resulting yellow solution is left to stir at room temperature. After 15 h, the reaction mixture is concentrated under reduced pressure. The residual trifluoroacetic acid is removed by treatment with toluene followed by concentration under reduced pressure twice. The resulting crude acid 35 is isolated as a yellow oil which solidifies upon standing.

To a flask containing the above acid is added 8 mL of acetic anhydride. The material

dissolves and a precipitant quickly forms. The mixture is stirred at room temperature overnight. The reaction is treated with methanol and concentrated under reduced pressure. This concentration procedure is repeated with methanol and twice with toluene. The residue is then purified by flash column chromatography on silica gel eluting with 40% to 60% ethyl acetate in
5 hexane to afford 165 mg of the title compound as a white solid.

Physical characteristics are as follows:

^1H NMR δ 7.3-7.0, 5.70, 3.64, 3.16, 2.94, 2.04;

EI-MS: $[M^+]=320$;

Anal. Found: C, 78.81; H, 6.19.

10 EXAMPLE 79 3-(1-Benzyl-2-phenyl-ethyl)-6-(2-cyclopropyl-1-cyclopropylmethyl-ethyl)-4-hydroxy-pyran-2-one (Formula R-6) Refer to Chart R.

To a flame-dried flask under an argon atmosphere is added 0.23 mL of distilled diisopropylamine and 1.6 mL of dry tetrahydrofuran. The solution is cooled to -78°C and treated with 1.0 mL (1.6 M in hexane) of *n*-butyllithium. The solution is warmed to 0°C for 15
15 min, then cooled to -35°C . The lithium diisopropylamine solution is treated with 160 mg of 3-(1-benzyl-2-phenyl-ethyl)-4-hydroxy-6-methyl-pyran-2-one (title product of Preparation 43) as a solution in 2.5 mL of tetrahydrofuran. The solution is stirred for 20 min as the bath temperature rises to -25°C . The solution is then treated with 0.12 mL of (bromomethyl)cyclopropane. The reaction mixture is allowed to warm to 0°C over 2 h. The reaction is then quenched with
20 excess 1 N aqueous hydrochloric acid and partitioned with diethyl ether. The aqueous phase is extracted with two additional portions of diethyl ether. The combined organic layers are dried (magnesium sulfate) and then concentrated under reduced pressure. The residue is purified by flash column chromatography on silica gel eluting with 20% to 40% ethyl acetate in hexane to afford 56 mg of the title product as a clear, colorless oil.

25 Physical characteristics are as follows:

^1H NMR δ 7.3-7.0, 6.05, 3.62, 3.22, 3.02, 2.52, 1.46, 0.5-0.2, 0.0- -0.15;

EI-MS: $[M^+]=428.2359$ found.

EXAMPLES 80-123

Following procedures analogous to those described above and using starting materials
30 and reagents readily known and available to one of ordinary skill in the art of organic synthesis, the following additional compounds of the present invention, having the mass spectral data indicated in Table III below, are prepared:

EXAMPLE 80 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(1-isobutyl-3-methyl-butyl)-pyran-2-one

35 EXAMPLE 81 6-(2-Cyclopropylmethyl-ethyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one

- EXAMPLE 82 3-Dicyclopropylmethyl-4-hydroxy-6-phenethyl-pyran-2-one
- EXAMPLE 83 6-(1-Cyclopropyl-ethyl)-3-dicyclopropylmethyl-4-hydroxy-pyran-2-one
- EXAMPLE 84 6-(1-Cyclopropyl-1-cyclopropylmethyl-ethyl)-3-dicyclopropylmethyl-4-hydroxy-pyran-2-one
- 5 EXAMPLE 85 6-(1-Cyclohexylmethyl-propyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one
- EXAMPLE 86 6-(1-Benzyl-propyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one
- EXAMPLE 87 6-(2-Cyclopropyl-1-cyclopropylmethyl-ethyl)-4-hydroxy-3(1-phenyl-propyl)-pyran-2-one
- 10 EXAMPLE 88 6-(1-Benzyl-2-cyclopropyl-ethyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one
- EXAMPLE 89 6-(2-Cyclopropyl-ethyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one
- EXAMPLE 90 6-(1-Cyclopropylmethyl-propyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one
- 15 EXAMPLE 91 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(4-phenyl-butyl)-pyran-2-one
- EXAMPLE 92 3-(Cyclohexyl-cyclopropyl-methyl)-6-(2-cyclopropyl-1-cyclopropylmethyl-ethyl)-4-hydroxy-pyran-2-one
- EXAMPLE 93 3-(Cyclopropyl-phenyl-methyl)-6-(1-ethyl-4-phenyl-butyl)-4-hydroxy-pyran-2-one
- EXAMPLE 94 6-(3-Cyclohexyl-propyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one
- 20 EXAMPLE 95 6-(3-Cyclohexyl-1-ethyl-propyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one
- EXAMPLE 96 6-(2-Cyclopropyl-ethyl)-4-hydroxy-3-(1-phenyl-propyl)-pyran-2-one
- EXAMPLE 97 6-(1-Allyl-but-3-enyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one
- EXAMPLE 98 6-But-3-enyl-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one
- 25 EXAMPLE 99 3-(Cyclopropyl-phenyl-methyl)-6-(1-ethyl-3-phenyl-propyl)-4-hydroxy-pyran-2-one
- EXAMPLE 100 5-Bromo-6-(2-cyclopropyl-ethyl)-4-hydroxy-3-(1-phenyl-propyl)-pyran-2-one
- EXAMPLE 101 6-(1-Benzyl-2-phenyl-ethyl)-4-hydroxy-3-(1-phenyl-propyl)-pyran-2-one
- 30 EXAMPLE 102 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(3-(2-methoxy-ethoxy)-propyl)-pyran-2-one
- EXAMPLE 103 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-5-(2-(2-methoxy-ethoxy)-ethyl)-6-(3-(2-methoxy-ethoxy)-pyran-2-one
- EXAMPLE 104 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-propyl-pyran-2-one
- 35 EXAMPLE 105 5-Bromo-4-hydroxy-6-phenylethyl-3(1-phenyl-propyl)-pyran-2-one
- EXAMPLE 106 3-(Cyclopropyl-phenyl-methyl)-6-(1-ethyl-3-(2-methoxy-ethoxy)-propyl)-

- 4-hydroxy-pyran-2-one
- EXAMPLE 107 6-(1-Benzyl-3-(2-methoxy-ethoxy)-propyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one
- EXAMPLE 108 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(3-(2-methoxy-ethoxy)-ethoxy)-pyran-2-one
- 5 EXAMPLE 109 5-Bromo-4-hydroxy-3-(1-phenyl-propyl)-6-propyl-pyran-2-one
- EXAMPLE 110 3-(Cyclopropyl-phenyl-methyl)-6-(1-ethyl-propyl)-4-hydroxy-5-(2-(2-methoxy-ethoxy)ethyl)-pyran-2-one
- EXAMPLE 111 6-(1-Benzyl-propyl)-5-bromo-4-hydroxy-3-(1-phenyl-propyl)-pyran-2-one
- 10 EXAMPLE 112 6-(2-Cyclopropyl-1-cyclopropylmethyl-ethyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-5-(2-(2-methoxy-ethoxy)-ethoxy)-ethyl-pyran-2-one
- EXAMPLE 113 12-Hydroxy-11-(1-phenyl-allyl)-1,4,9-trioxa-dispiro[4.2.5.2]pentadec-11-en-10-one
- EXAMPLE 114 12-Hydroxy-11-(1-phenyl-propyl)-1,4,9-trioxa-dispiro[4.2.5.2]pentadec-11-en-10-one
- 15 EXAMPLE 115 4-Hydroxy-3-(1-phenyl-propyl)-1-oxa-spiro[5.5]undec-3-ene-2,9-dione
- EXAMPLE 116 4,9-Dihydroxy-3-(1-phenyl-propyl)-1-oxa-spiro[5.5]undec-3-en-2-one
- EXAMPLE 117 3-(Cyclopropyl-phenyl-methyl)-6-(2-furan-2-yl-2-hydroxy-ethyl)-4-hydroxy-pyran-2
- 20 Physical characteristics are as follows:
MS: m/z (relative intensity) 352 (3, parent), 334 (27), 256 (100), 131 (30), 121 (36), 118 (21).
- EXAMPLE 118 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(4,4,4-trifluoro-butyl)-pyran-2-one
- 25 Physical characteristics are as follows:
MS: m/z (relative intensity) 352 (87, parent), 261 (78), 235 (80), 131 (88), 144 (53), 115 (68).
- EXAMPLE 119 6-[2-(1-Cyclohexyl-1H-tetrazol-5-yl)-ethyl]-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-2-one
- 30 Physical characteristics are as follows:
MS: m/z (relative intensity) 420 (48, parent), 221 (45), 172 (46), 125 (46), 115 (52), 91 (71), 85 (100), 83 (45), 69 (56).
- EXAMPLE 120 6,6-Dibenzyl-4-hydroxy-3-(1-phenyl-propyl)-5,6-dihydro-pyran-2-one
- Physical characteristics are as follows:
35 MS: 412.2032 Found.
¹H-NMR: 7.5-7.0, 4.11, 3.1-2.8, 2.42, 2.09, 0.95.

EXAMPLE 121 4-Hydroxy-3-(1-phenyl-allyl)-1,9-dioxaspiro[5.5]undec-3-en-2-one

Physical characteristics are as follows:

MS m/e (relative intensity): 117 (100), 129 (65), 175 (36), 256 (14), 282 (22), 300 (11).

NMR (CDCl₃, TMS): 7.3-7.5, 6.8, 6.3, 5.0-5.5, 3.7-3.9, 2.5, 1.5-1.9.

5 EXAMPLE 122 4-Hydroxy-6-methyl-3-(3-phenyl-prop-2-enyl)-2H-Pyran-2-one

Physical characteristics are as follows:

¹H-NMR: 7.4-7.1, 6.4-6.1, 6.0, 3.15, 2.14

EXAMPLE 123 4-Hydroxy-3-(1-phenyl-propyl)-1-oxa-spiro[5.5]undec-3-ene-2,9-dione
monooxime

10 Physical characteristics are as follows:

Mp 209-211 °C (decomposed).

MS: m/e (relative intensity): 329 (28), 267 (7), 212 (7), 176 (19), 159 (40), 119 (84), 91
(100).

PREPARATION 44 4-Hydroxy-3-(1-phenylcyclobutyl)-6-phenethyl-2H-pyran-2-one

15 (Formula S-3) Refer to Chart S.

This compound is prepared by the procedures described in Example 1 above.

Physical characteristics are as follows:

M.P.: 215-216 °C.

Anal. found: C, 79.37; H, 6.33.

20 EXAMPLE 124 4-Hydroxy-3-(1-phenylcyclobutyl)-6-[1-(phenylmethyl)propyl]-2H-pyran-
2-one (Formula S-4) Refer to Chart S.

This compound is prepared by procedures described in Example 6 above.

Physical characteristics are as follows:

EI HRMS: found 374.1877.

25 ¹H NMR(CDCl₃): δ 0.79, 1.5-1.6, 1.7-2.0, 2.1, 2.47, 2.7-2.9, 5.97, 7.0-7.3, 7.7.

PREPARATION 45 4-Hydroxy-1-oxaspiro[5.7]tridec-3-en-2-one (Formula T-3) Refer to
Chart T.

This compound is prepared by procedures described in Preparation 16A above.

Physical characteristics are as follows:

30 M.P.: 128-130 °C.

Anal. found: C, 68.44; H, 8.7.

PREPARATION 46 4-Hydroxy-3(1-phenyl-3-trimethylsilyl-2E-propenyl)-1-oxaspiro(5-
.7)tridec-3-en-2-one (Formula T-4) Refer to Chart T.

This compound is prepared by procedures described in Preparation 16B above.

35 Physical characteristics are as follows:

¹H NMR(CDCl₃): δ 0.7, 1.0-2.1, 2.4-2.5, 3.5, 4.3, 4.4, 5.0, 5.6-5.9, 6.4-6.6, 7.1-7.3.

-100-

EXAMPLE 125 4-Hydroxy-3-(1-phenyl-2-propenyl)-1-oxaspiro[5.7]tridec-3-en-2-one
(Formula T-5) Refer to Chart T.

This compound is prepared by procedures described in Preparation 16C above.

Physical characteristics are as follows:

5 M.P.: 152-153 °C.

EI HRMS: found 326.1894.

EXAMPLE 126 4-Hydroxy-3-(1-phenylpropyl)-1-oxaspiro[5.7]tridec-3-en-2-one (Formula
T-6) Refer to Chart T.

This compound is prepared by procedures described in Preparation 16D above.

10 Physical characteristics are as follows:

M.P.: 166.5-167 °C.

EI HRMS: found 328.2039.

EXAMPLES 127-130

Following procedures analogous to those described in Chart L, the following compounds
15 of the present invention are prepared:

EXAMPLE 127 4-Hydroxy-3-(1-phenylallyl)-1-oxa-spiro[5.6]-dodec-3-en-2-one

Physical characteristics are as follows:

M.P.: 120-121 °C.

EXAMPLE 128 4-Hydroxy-3-(1-phenylallyl)-1-oxa-spiro[5.4]-dec-3-en-2-one

20 Physical characteristics are as follows:

M.P.: 115-117 °C.

EXAMPLE 129 7-Benzyl-4-hydroxy-3-(1-phenylallyl)-1-oxa-spiro[5.5]undec-3-en-2-one

Physical characteristics (of mixture of diastereomers at 1-phenylallyl center) are as
follows:

25 MS m/e (rel %): 388, 370, 297, 279, 172, 171, 117, 115.

HRMS found: 388.2033.

EXAMPLE 130 4-Hydroxy-3-(1-phenylpropyl)-1-oxa-spiro[5.4]-dec-3-en-2-one

Physical characteristics are as follows:

M.P.: 158-161 °C.

30 EXAMPLES 131-145

Following procedures analogous to those described above, the following compounds of
the present invention are prepared:

EXAMPLE 131 3-(Cyclopropylphenylmethyl)-6-[1-ethyl-3-(4-morpholinyl)propyl]-4-
hydroxy-2H-pyran-2-one

35 Physical characteristics are as follows:

HRMS found = 397.2253.

-101-

EXAMPLE 132 3-(Cyclopropylphenylmethyl)- β -ethyl-4-hydroxy-2-oxo-, phenylmethyl ester 2H-pyran-6-propanoic acid

Physical characteristics are as follows:

HRMS found = 432.1926.

5 EXAMPLE 133 3-(Cyclopropylphenylmethyl)-4-hydroxy-6-[2-methyl-1-(phenylmethyl)propyl]-2H-pyran-2-one

Physical characteristics are as follows:

HRMS found = 389.2108.

EXAMPLE 134 3-(Cyclopropylphenylmethyl)-4-hydroxy-6-[2-methyl-1-((tetrahydro-2H-pyran-3-yl)methyl)propyl]-2H-pyran-2-one

Physical characteristics are as follows:

HRMS found = 396.2309.

EXAMPLE 135 4-Hydroxy-3-(1-phenylpropyl)-6-[1-((tetrahydro-2H-pyran-3-yl)methyl)propyl]-2H-pyran-2-one

Physical characteristics are as follows:

HRMS found = 370.2139.

EXAMPLE 136 3-(Cyclopropylphenylmethyl)-6-(1-ethyl-4,4,4-trifluorobutyl)-4-hydroxy-2H-pyran-2-one

Physical characteristics are as follows:

HRMS found = 380.1588

Anal. Found: C, 66.34; H, 6.27.

EXAMPLE 137 3-[2-[3-(Cyclopropylphenylmethyl)-4-hydroxy-2-oxo-2H-pyran-6-yl]butyl]-1-[(4-methylphenyl)sulfonyl]-piperidine

Physical characteristics are as follows:

HRMS found = 536.2482

Anal. Found: C, 69.40; H, 7.04; N, 2.21.

EXAMPLE 138 2-[2-[3-(Cyclopropylphenylmethyl)-4-hydroxy-2-oxo-2H-pyran-6-yl]butyl]-1-[(4-methylphenyl)sulfonyl]-pyrrolidine

Physical characteristics are as follows:

HRMS found = 521.2229

Anal. Found: C, 68.45; H, 6.81; N, 2.35.

EXAMPLE 139 3-(Cyclopropylphenylmethyl)-4-hydroxy-6-(3,3,3-trifluoropropyl)-2H-pyran-2-one

Physical characteristics are as follows:

HRMS found = 338.1143

Anal. Found: C, 63.22; H, 5.28.

EXAMPLE 140 2-[2-[3-(Cyclopropylphenylmethyl)-4-hydroxy-2-oxo-2H-pyran-6-yl]butyl]-1-[(4-methylphenyl)sulfonyl]-piperidine

Physical characteristics are as follows:

HRMS found = 535.2398

5 Anal. Found: C, 68.74; H, 7.10; N, 2.36.

EXAMPLE 141 4-[2-[3-(Cyclopropylphenylmethyl)-4-hydroxy-2-oxo-2H-pyran-6-yl]butyl]-1-[(4-methylphenyl)sulfonyl]-piperidine

Physical characteristics are as follows:

HRMS found = 535.2394.

10 EXAMPLE 142 4-[2-[3-(Cyclopropylphenylmethyl)-4-hydroxy-2-oxo-2H-pyran-6-yl]butyl]-1-(phenylmethyl)-2-pyrrolidinone

Physical characteristics are as follows:

HRMS found = 471.2414.

EXAMPLE 143 6-(Cyclopentylmethyl)-3-(cyclopropylphenylmethyl)-4-hydroxy-2H-pyran-2-one

15

Physical characteristics are as follows:

HRMS found = 324.1736

Anal. Found: C, 77.49; H, 7.37.

EXAMPLE 144 3-(Cyclopropylphenylmethyl)-4-hydroxy-6-[(tetrahydro-2H-pyran-4-yl)methyl]-2H-pyran-2-one

20

Physical characteristics are as follows:

HRMS found = 340.1672

Anal. Found: C, 73.90; H, 7.55.

EXAMPLE 145 3-(Cyclopropylphenylmethyl)-6-(3-fluoropropyl)-4-hydroxy-2H-pyran-2-one

25

Physical characteristics are as follows:

HRMS found = 302.1311

Anal. Found: C, 70.85; H, 6.36.

EXAMPLES 146-153

30 The following procedures analogous to those described above, the following compounds of the present invention are prepared:

EXAMPLE 146 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(α -ethyl- β -hydroxyphenethyl)-2H-pyran-2-one (Formula TT-4) Refer to Chart TT.

Physical characteristics are as follows:

35 MP 73-90°C

EXAMPLE 147 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(β -hydroxy-p-methylphenethyl)-

2H-pyran-2-one. Refer to Chart TT.

Physical characteristics are as follows:

MP 87-9°C

EXAMPLE 148 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(β -hydroxy-p-fluorophenethyl)-2H-pyran-2-one. Refer to Chart TT.

Physical characteristics are as follows:

MP 68-73°C

EXAMPLE 149 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(β -hydroxy-p-chlorophenethyl)-2H-pyran-2-one. Refer to Chart TT.

Physical characteristics are as follows:

MP 76-79°C

EXAMPLE 150 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(β -hydroxy-m-chlorophenethyl)-2H-pyran-2-one. Refer to Chart TT.

Physical characteristics are as follows:

MP 62-75°C

EXAMPLE 151 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(β -hydroxy-o-chlorophenethyl)-2H-pyran-2-one. Refer to Chart TT.

Physical characteristics are as follows:

MP 65-78°C

EXAMPLE 152 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(2-(furan-3-yl)-2-hydroxyethyl)-2H-pyran-2-one. Refer to Chart TT.

Physical characteristics are as follows:

MP 66-78°C

EXAMPLE 153 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(2-(thiophen-3-yl)-2-hydroxyethyl)-2H-pyran-2-one. Refer to Chart TT.

Physical characteristics are as follows:

MP 71-89°C

EXAMPLES 154-167

The following procedures are analogous to those described in Chart H, but using Q-1 (see Chart Q) as the starting material, the following compounds are prepared:

EXAMPLE 154 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(α -ethyl-p-fluorophenethyl)-2H-pyran-2-one

Physical characteristics are as follows:

MP 52-63°C

EXAMPLE 155 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(α -ethyl-p-chlorophenethyl)-2H-pyran-2-one

acteristics are as follows:

3-(α -cyclopropylbenzyl)-4-hydroxy-6-(α -ethyl-m-chlorophenethyl)-2H-pyran-2-one

acteristics are as follows:

3-(α -cyclopropylbenzyl)-4-hydroxy-6-(α -ethyl-o-chlorophenethyl)-2H-pyran-2-one

acteristics are as follows:

3-(α -cyclopropylbenzyl)-4-hydroxy-6-(α -ethyl-p-bromophenethyl)-2H-pyran-2-one

acteristics are as follows:

3-(α -cyclopropylbenzyl)-4-hydroxy-6-(α -ethyl-m-bromophenethyl)-2H-pyran-2-one

acteristics are as follows:

3-(α -cyclopropylbenzyl)-4-hydroxy-6-(α -ethyl-p-trifluoromethylphenethyl)-2H-pyran-2-one

acteristics are as follows:

3-(α -cyclopropylbenzyl)-4-hydroxy-6-(α -ethyl-m-trifluoromethylphenethyl)-2H-pyran-2-one

acteristics are as follows:

3-(α -cyclopropylbenzyl)-4-hydroxy-6-(α -ethyl-o-trifluoromethylphenethyl)-2H-pyran-2-one

acteristics are as follows:

3-(α -cyclopropylbenzyl)-4-hydroxy-6-(α -ethyl-p-methoxyphenethyl)-2H-pyran-2-one

acteristics are as follows:

3-(α -cyclopropylbenzyl)-4-hydroxy-6-(α -ethyl-m-methoxyphenethyl)-2H-pyran-2-one

Physical characteristics are as follows:

MP 42-57°C

EXAMPLE 165 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(p-fluorophenethyl)-2H-pyran-2-one

5 Physical characteristics are as follows:

oil

EXAMPLE 166 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(p-chlorophenethyl)-2H-pyran-2-one

Physical characteristics are as follows:

10 MP 64-78°C

EXAMPLE 167 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(p-bromophenethyl)-2H-pyran-2-one

Physical characteristics are as follows:

MP 56-68°C

15 PREPARATION 47 5,6-Dihydro-4-hydroxy-6-phenyl-6-phenylmethyl-2H-pyran-2-one
(Formula VV-1; R₁ = phenyl, R₂ = phenylmethyl) Refer to Chart VV.

Deoxybenzoin (3.1 g) is converted to the title compound using the general procedure for synthesis of 5,6-dihydropyrones of Preparation 16, A. Flash chromatography of the residue with hexanes/ether (2:1, 1:1) followed by ether gives 3.6 g of the title compound as a white solid.

20 Physical characteristics are as follows:

MP 89-92 °C.

¹H NMR (300 MHz, CDCl₃): δ 2.75-2.89, 3.09-3.19, 3.28-3.39, 7.06-7.08, 7.25-7.28, 7.35-7.39.

M/S m/e (rel %): 190(8), 189 (65), 147 (10), 105 (100), 77 (30).

25 Anal. Found: C, 77.09; H, 5.78.

PREPARATION 48 5,6-Dihydro-4-Hydroxy-6-phenethyl-6-propyl-2H-pyran-2-one (Formula VV-1; R₁ = phenethyl, R₂ propyl) Refer to Chart VV.

1-Phenyl-3-hexanone (2.0 g) is converted to the title compound using the general procedure for synthesis of 5,6-dihydropyrones of Preparation 16, A. to yield 1.96 g of the title
30 compound as a light yellow oil.

Physical characteristics are as follows:

¹H NMR (300 MHz, CDCl₃): δ 0.96, 1.21, 1.48, 1.72, 1.98, 2.73, 3.43, 7.15-7.32.

Anal. Found: C, 73.77; H, 7.96.

PREPARATION 49 5,6-Dihydro-4-hydroxy-6-phenylmethyl-6-propyl-2H-pyran-2-one
35 (Formula VV-1; R₁ = phenylmethyl, R₂ = propyl) Refer to Chart VV.

1-Phenyl-2-pentanone (2 g) is converted to the title compound using the general

procedure for synthesis of 5,6-dihydropyrones of Preparation 16. A. to yield 2.1 g of the title compound as a white solid.

Physical characteristics are as follows:

MP 101-103 °C.

5 ¹H NMR (300 MHz, CDCl₃): δ 0.97, 1.51, 1.72, 2.62, 2.84-2.91, 3.11-3.27, 7.12-7.34.

EXAMPLE 168 5,6-Dihydro-4-hydroxy-6-phenyl-6-(phenylmethyl)-3-(1-phenyl-2-propenyl)-2H-pyran-2-one (Formula VV-4; R₁ = phenyl, R₂ = phenylmethyl) Refer to Chart VV.

5,6-Dihydro-4-hydroxy-6-phenyl-6-phenylmethyl-2H-pyran-2-one (0.2 g) of Preparation 10 47 is reacted with methyl (1-phenyl-3-trimethylsilyl-2E-propenyl) carbonate (VV-2) of Preparation 17, using the general procedure for palladium catalyzed alkylation of Preparation 16. B. Desilylation using the general procedure in Preparation 16, C. provides 0.14 g of the title compound as a white foam.

Physical characteristics are as follows:

15 ¹H NMR complicated by presence of diastereomers.

¹H NMR (300 MHz, CDCl₃): δ 2.79-3.39, 4.31, 4.83-5.15, 5.34, 5.90-5.99, 6.03, 6.23-6.31, 6.50-6.54, 6.87-7.34.

HRMS found: 397.1794.

EXAMPLE 169 5,6-Dihydro-4-hydroxy-6-phenyl-6-(phenylmethyl)-3-(1-phenylpropyl)-20 2H-pyran-2-one (Formula VV-5; R₁ = phenyl, R₂ = phenylmethyl) Refer to Chart VV.

The title compound of Example 168, 5,6-Dihydro-4-hydroxy-6-phenyl-6-(phenylmethyl)-3-(1-phenyl-2-propenyl)-2H-pyran-2-one, (47 mg) is hydrogenated using the general procedure in Preparation 16, D, utilizing 10% palladium/carbon as catalyst, to yield 47 mg of the title 25 compound as a white foam.

Physical characteristics are as follows:

¹H NMR complicated by presence of diastereomers.

¹H NMR (300 MHz, CDCl₃): δ 0.42, 0.95, 1.30-2.10, 2.77, 2.98, 3.14, 3.33, 3.91, 4.13, 5.48, 5.03, 6.86-6.92, 6.93-7.07, 7.08-7.49.

30 HRMS found: 399.1598.

EXAMPLE 170 3-(1,3-Diphenyl-2-propenyl)-5,6-dihydro-4-hydroxy-6-(2-phenylethyl)-6-propyl-, (E)-2H-pyran-2-one (Formula WW-3; R₁ = phenethyl, R₂ = propyl) Refer to Chart WW.

To a solution of 5,6-dihydro-4-hydroxy-6-phenethyl-6-propyl-2H-pyran-2-one (100 mg) 35 of Preparation 48 and 1,3-diphenyl allyl alcohol (WW-2) (161 mg) in dioxane, under argon, is added boron trifluoride-diethyl ether (237 μL). The reaction mixture is stirred at room

-107-

temperature for 5 min. and then quenched with water. Ether is added and the combined organic layers are extracted with 0.1 N sodium hydroxide (3 x 10 mL). The combined aqueous layers are cooled to 0°C and acidified to pH 1 by the dropwise addition of 2 N hydrochloric acid. The milky solution is extracted with methylene chloride (3x 15 mL) and the combined organic layers are washed with sat. sodium chloride, dried (sodium sulfate) and evaporated under reduced pressure to give 155 mg of the title compound as a white foam.

Physical characteristics are as follows:

¹H NMR complicated by presence of diastereomers.

¹H NMR (300 MHz, CDCl₃): δ 0.90-1.02, 1.38-1.53, 1.73-2.18, 2.49-2.75, 5.23, 6.36-6.75, 7.04-7.41.

MS m/e (rel %): 453 (20), 331 (17), 201 (39), 175 (33), 173 (16), 115 (30), 105 (19), 91 (100).

EXAMPLE 171 3-(1,3-Diphenylpropyl)-5,6-dihydro-4-hydroxy-6-(2-phenylethyl)-6-propyl-, 2H-pyran-2-one (Formula WW-4; R₁ = phenethyl, R₂ = propyl)

Refer to Chart WW.

The title compound of Example 170, 3-(1,3-Diphenyl-2-propenyl)-5,6-dihydro-4-hydroxy-6-(2-phenylethyl)-6-propyl-, (E)-2H-pyran-2-one, (100 mg) is hydrogenated using the general procedure in Preparation 16, D, utilizing 10% palladium/carbon as catalyst, to yield 100 mg of the title compound as a white foam.

Physical characteristics are as follows:

¹H NMR complicated by presence of diastereomers.

¹H NMR (300 MHz, CDCl₃): δ 0.72-1.03, 1.17-2.78, 4.36, 5.84, 6.97-7.45.

HRMS found: 455.2609.

EXAMPLE 172 3-(1,3-Diphenyl-2-propenyl)-5,6-dihydro-4-hydroxy-6-phenyl-6-(phenylmethyl)-2H-pyran-2-one (Formula WW-3; R₁ = phenyl, R₂ = phenylmethyl) Refer to Chart WW.

To a solution of 5,6-dihydro-4-hydroxy-6-phenyl-6-phenylmethyl-2H-pyran-2-one (200 mg) of Preparation 47 and 1,3-diphenyl allyl alcohol (WW-2) (300 mg) in dioxane, under argon, is added boron trifluoride-diethyl ether (440 µL). The reaction mixture is stirred at room temperature for 5 min. and then quenched with water. Ether is added and the combined organic layers are extracted with 0.1 N sodium hydroxide (3x 10 mL). The combined aqueous layers are cooled to 0°C and acidified to pH 1 by the dropwise addition of 2 N hydrochloric acid. The milky solution is extracted with methylene chloride (3x 15 mL) and the combined organic layers are washed with sat. sodium chloride, dried (sodium sulfate) and evaporated under reduced pressure to give the title compound as a white foam.

Physical characteristics are as follows:

MP 181-185 °C (dec).

¹H NMR complicated by presence of diastereomers.

¹H NMR (300 MHz, CDCl₃): δ 2.82-2.88, 3.04-3.16, 3.30-3.39, 4.97, 5.09, 5.61, 5.66, 5.87, 6.18-6.26, 6.41, 6.52-6.60, 6.96-7.40.

5 MS m/e (rel %): 454 (27), 363 (44), 233 (39), 205 (28), 193 (100), 115 (94), 91 (75).

Anal. Found: C, 83.43; H, 5.90.

EXAMPLE 173 3-(1,2-Diphenylethenyl)-5,6-dihydro-4-hydroxy-6-(2-phenylethyl)-6-propyl-, (E)-2H-pyran-2-one (Formula XX-2; R₁ = phenethyl, R₂ = propyl) Refer to Chart XX.

10 To a solution of 5,6-dihydro-4-hydroxy-6-phenethyl-6-propyl-2H-pyran-2-one (100 mg) of Preparation 48 and stilbene oxide (151 mg) in dioxane, under argon, is added boron trifluoride-diethyl ether (237 µL). The reaction mixture is stirred at room temperature for 16 hr. and then quenched with water. Ether is added and the combined organic layers are extracted with 0.1 N sodium hydroxide (3x 10 mL). The combined aqueous layers are cooled to 0°C and
15 acidified to pH 1 by the dropwise addition of 2 N hydrochloric acid. The milky solution is extracted with methylene chloride (3x 15 mL) and the combined organic layers are washed with sat. sodium chloride, dried (sodium sulfate) and evaporated under reduced pressure to give the title compound as a white foam.

Physical characteristics are as follows:

20 ¹H NMR complicated by presence of diastereomers.

Physical characteristics are as follows:

¹H NMR (300 MHz, CDCl₃): δ 0.96, 1.29-1.46, 1.54-1.71, 1.80-2.04, 2.38, 2.59-2.71, 4.92, 5.78, 6.61, 7.13-7.41.

MS m/e (rel %): 439 (22), 438 (66), 247 (31), 220 (100), 105 (29), 91 (71).

25 HRMS Found: 439.2261.

EXAMPLE 174 5,6-Dihydro-4-hydroxy-6-(2-phenylethyl)-3-(1-phenyl-2-propenyl)-6-propyl-2H-pyran-2-one (Formula VV-4; R₁ = phenethyl, R₂ = propyl)
Refer to Chart VV.

30 5,6 Dihydro-4-hydroxy-6-phenethyl-6-propyl-2H-pyran-2-one (0.3 g) of Preparation 48 is reacted with methyl (1-phenyl-3-trimethylsilyl-2E-propenyl) carbonate (VV-2) of Preparation 17, using the general procedure for palladium catalyzed alkylation of Preparation 16, B. Desilylation using the general procedure in Preparation 16, C. provides 0.24 g of the title compound as a white foam.

Physical characteristics are as follows:

35 ¹H NMR complicated by presence of diastereomers.

¹H NMR (300 MHz, CDCl₃): δ 0.87-1.04, 1.34-1.55, 1.68-1.77, 1.77-2.14, 2.45-2.77,

5.06, 5.40-5.47, 6.30-6.45, 6.56, 6.62, 7.08, 7.19-7.38.

HRMS Found: 377.2128.

EXAMPLE 175 5,6-Dihydro-4-hydroxy-6-(2-phenylethyl)-3-(1-phenylpropyl)-6-propyl-
2H-pyran-2-one (Formula VV-5; R₁ = phenethyl, R₂ = propyl) Refer to
Chart VV.

The title compound of Example 174, 5,6-Dihydro-4-hydroxy-6-(2-phenylethyl)-3-(1-phenyl-2-propenyl)-6-propyl-2H-pyran-2-one, (69 mg) is hydrogenated using the general procedure in Preparation 16, D, utilizing 10% palladium/carbon as catalyst, to yield 66 mg of the title compound as a white foam.

Physical characteristics are as follows:

¹H NMR complicated by presence of diastereomers.

¹H NMR (300 MHz, CDCl₃): δ 0.87-1.13, 1.25-2.20, 2.33-2.54, 2.60-2.78, 4.23, 5.68, 7.13-7.42.

HRMS Found: 379.2264.

EXAMPLE 176 3-(1,3-Diphenyl-2-propenyl)-5,6-dihydro-4-hydroxy-6-(phenylmethyl)-6-propyl-2H-pyran-2-one (Formula WW-3; R₁ = phenylmethyl, R₂ = propyl) Refer to Chart WW.

To a solution of 5,6-dihydro-4-hydroxy-6-phenylmethyl-6-propyl-2H-pyran-2-one (200 mg) of Preparation 49 and 1,3-diphenyl allyl alcohol (WW-2) (341 mg) in dioxane, under argon, is added boron trifluoride-diethyl ether (200 μL). The reaction mixture is stirred at room temperature for 5 min. and then quenched with water. Ether is added and the combined organic layers are extracted with 0.1 N sodium hydroxide (3x 10 mL). The combined aqueous layers are cooled to 0°C and acidified to pH 1 by the dropwise addition of 2 N hydrochloric acid. The milky solution is extracted with methylene chloride (3x 15 mL) and the combined organic layers are washed with sat. sodium chloride, dried (sodium sulfate) and evaporated under reduced pressure to give the title compound as a white foam.

Physical characteristics are as follows:

¹H NMR complicated by presence of diastereomers.

¹H NMR (300 MHz, CDCl₃): δ 0.90, 1.40-1.76, 2.37-2.52, 2.95-3.18, 5.12, 5.24, 6.28-6.71, 7.11-7.45.

HRMS Found: 439.2274.

EXAMPLE 177 3-(1,3-Diphenylpropyl)-5,6-dihydro-4-hydroxy-6-(phenylmethyl)-6-propyl-2H-pyran-2-one (Formula WW-4; R₁ = phenylmethyl, R₂ = propyl) Refer to Chart WW.

The title compound of Example 176, 3-(1,3-Diphenyl-2-propenyl)-5,6-dihydro-4-hydroxy-6-(phenylmethyl)-6-propyl-2H-pyran-2-one, (62 mg) is hydrogenated using the general

procedure in Preparation 16, D, utilizing 10% palladium/carbon as catalyst, to yield 62 mg of the title compound as a white foam.

Physical characteristics are as follows:

¹H NMR complicated by presence of diastereomers.

5 ¹H NMR (300 MHz, CDCl₃): δ 0.90, 1.35-1.78, 2.36-2.61, 2.63-2.80, 2.95-3.10, 4.34, 5.71, 6.88-7.46.

HRMS Found: 441.2430.

EXAMPLE 178 3-(α-Cyclopropyl-*meta*-(phenylsulfonylamino)benzyl)-6-(α-ethylphenethyl)-4-hydroxy-2H-pyran-2-one (Formula M-7 wherein R₁ is
10 phenyl) Refer to Chart M.

To a cold (0°) stirred solution of 65 mg of amine (M-5) is added 27 μL of pyridine, followed by 23 μL of benzenesulfonyl chloride. The solution is stirred and allowed to warm slowly to room temperature. After 18 hours, it is diluted with ethyl acetate, and the solution washed with dilute aqueous hydrochloric acid and brine, and dried over magnesium sulfate. The
15 solution is concentrated under reduced pressure, and the residue flash chromatographed on silica gel using 10-15% ethyl acetate in dichloromethane to provide 66.7 mg of title compound as a white foam.

Physical characteristics are as follows:

20 ¹H NMR δ 0.098, 0.24, 0.45, 0.6, 0.78, 1.55, 1.95, 2.49, 2.75, 2.84, 3.40, 5.84, 6.87, 7.0-7.5, 7.70.

IR 3253, 2964, 2661, 1572, 1414, 1284, 1158, 731 cm⁻¹

TLC R_f 0.23 (10% ethyl acetate in dichloromethane).

HRMS m+ at m/z 529.1927; calc'd 529.1923.

EXAMPLES 179-185

25 Utilizing procedures analogous to those described above in Example 178, the following additional compounds of the present invention are prepared:

EXAMPLE 179 3-(α-Cyclopropyl-*meta*-(propylsulfonylamino)benzyl)-6-(α-ethylphenethyl)-4-hydroxy-2H-pyran-2-one

Physical characteristics are as follows:

30 M+ 495.2074.

EXAMPLE 180 3-(α-Cyclopropyl-*meta*-((E)-2-phenylethenylsulfonylamino)benzyl)-6-(α-ethylphenethyl)-4-hydroxy-2H-pyran-2-one

Physical characteristics are as follows:

M+ 555.2088.

35 EXAMPLE 181 3-(α-Cyclopropyl-*meta*-(4-bromophenylsulfonylamino)benzyl)-6-(α-ethylphenethyl)-4-hydroxy-2H-pyran-2-one

-111-

Physical characteristics are as follows:

M+ 607.1023.

XAMPLE 182 3-(α -Cyclopropyl-*meta*-(2,5-dichlorophenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one

Physical characteristics are as follows:

M+ 597.1143.

XAMPLE 183 3-(α -Cyclopropyl-*meta*-(4-*tert*-butylphenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one

Physical characteristics are as follows:

M+ 585.2558.

XAMPLE 184 3-(α -Cyclopropyl-*meta*-(4-cyanophenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one

Physical characteristics are as follows:

M+ 554.

XAMPLE 185 3-(α -Cyclopropyl-*meta*-(4-methoxyphenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one

Physical characteristics are as follows:

M+ 559.

XAMPLE 186 3- α -Ethylbenzyl-6- α -ethylbenzyl-4-hydroxy-2H-pyran-2-one

Physical characteristics are as follows:

^1H NMR (300 MHz, CDCl_3) δ 7.44, 7.23-7.09, 6.08, 4.17, 3.31, 2.24-2.10, 1.95, 1.75, 0.89, 0.74.

PREPARATION 50 4-Hydroxy-6-methyl-3-(α -methylbenzyl)-2H-pyran-2-one (Formula Y-5)
Refer to Chart Y. Following the procedure of Chart Y, 0.743 grams of Y-5 was obtained.

Physical characteristics are as follows:

H-NMR: 1.64, 2.12, 4.50, 5.99, 7.2, 7.35.

PREPARATION 51 4-Hydroxy-3-(α -(R)-ethylbenzyl)-6-methyl-2H-pyran-2-one (Formula Z-5)
Refer to Chart Z. Following the procedure of Chart Z, 0.160 grams of Z-5 was obtained.

Physical characteristics are as follows:

H-NMR: 0.92, 2.1, 2.2, 4.2, 6.1, 7.2, 7.4.

EXAMPLE 187 3-([R]- α -ethylbenzyl)-4-hydroxy-6-([R]- α -ethylphenethyl)-2H-pyran-2-one (Formula AA-5) Refer to Chart AA.

EXAMPLE 188 3-([R]- α -ethylbenzyl)-4-hydroxy-6-([S]- α -ethylphenethyl)-2H-pyran-2-

-112-

one (Formula BB-5) Refer to Chart BB.

EXAMPLE 189 3-([S]- α -ethylbenzyl)-4-hydroxy-6-([R]- α -ethylphenethyl)-2H-pyran-2-one (Formula CC-5) Refer to Chart CC.

EXAMPLE 190 3-([S]- α -ethylbenzyl)-4-hydroxy-6-([S]- α -ethylphenethyl)-2H-pyran-2-one (Formula DD-5) Refer to Chart DD.

EXAMPLE 191 3-([R]- α -ethylbenzyl)-4-hydroxy-6-([R]- α -ethylphenethyl)-2H-pyran-2-one (Formula EE-5) Refer to Chart EE.

EXAMPLE 192 3-([R]- α -ethylbenzyl)-4-hydroxy-6-([S]- α -ethylphenethyl)-2H-pyran-2-one (Formula FF-3) Refer to Chart FF.

EXAMPLE 193 3-([S]- α -ethylbenzyl)-4-hydroxy-6-([R]- α -ethylphenethyl)-2H-pyran-2-one (Formula GG-5) Refer to Chart GG.

EXAMPLE 194 3-([S]- α -ethylbenzyl)-4-hydroxy-6-([S]- α -ethylphenethyl)-2H-pyran-2-one (Formula HH-3) Refer to Chart HH.

EXAMPLE 195 Refer to Chart II.

3-(α -cyclopropyl((5-methoxymethylhydroxymethylether)furfur-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one (Formula II-7)

Physical characteristics are as follows:

H-NMR: 0.3, 0.4-0.7, 0.9, 1.3, 1.6, 2.5, 2.9, 3.3, 3.8, 4.4, 4.6, 5.65, 5.68, 6.2, 6.3, 7.1-

7.3.

3-(α -cyclopropyl((5-hydroxymethyl)furfur-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one (Formula II-8)

EXAMPLE 196 Refer to Chart JJ.

3-(α -cyclopropyl((5-methoxymethyl)furfur-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one (Formula JJ-2)

3-(α -cyclopropyl((5-azidomethyl)furfur-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one (Formula JJ-3)

3-(α -cyclopropyl((5-aminomethyl)furfur-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one (Formula JJ-4)

3-(α -cyclopropyl((5-[N-acetyl]aminomethyl)furfur-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one (Formula JJ-5)

3-(α -cyclopropyl((5-[N-phenylsulphonyl]aminomethyl)furfur-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one (Formula JJ-6)

The following compounds are prepared using the procedures of Chart JJ, but with a substituted sulphonyl halide:

3-(α -cyclopropyl((5-[N-(o-fluoro)phenylsulphonyl]aminomethyl)furfur-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one

-113-

3-(α -cyclopropyl((5-[N-(p-fluoro)phenylsulphonyl]aminomethyl)furfur-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one
 3-(α -cyclopropyl((5-[N-(m-fluoro)phenylsulphonyl]aminomethyl)furfur-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one
 3-(α -cyclopropyl((5-[N-(o-fluoro)phenylsulphonyl]aminomethyl)furfur-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one
 3-(α -cyclopropyl((5-[N-(o-cyano)phenylsulphonyl]aminomethyl)furfur-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one
 3-(α -cyclopropyl((5-[N-(p-cyano)phenylsulphonyl]aminomethyl)furfur-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one
 3-(α -cyclopropyl((5-[N-(m-cyano)phenylsulphonyl]aminomethyl)furfur-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one
 3-(α -cyclopropyl((5-[N-(m-cyano)phenylsulphonyl]aminomethyl)furfur-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one
 3-(α -cyclopropyl((5-(4-carboethoxy-1,2,3-triazol-1-yl)methyl)furfur-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one (Formula JJ-7)
 3-(α -cyclopropyl((5-(4-carboxylic-1,2,3-triazol-1-yl)methyl)furfur-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one (prepared by hydrolyzing JJ-7 to its corresponding carboxylic acid)

EXAMPLE 197

Refer to Chart KK.

3-(α -cyclopropyl((5-(N-(1-nitro-2-methylthioethen-2-yl)aminomethyl)furfur-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one (Formula KK-3)
 3-(α -cyclopropyl((5-(N-(1-nitro-2-[N-isopropyl]ethen-2-yl)aminomethyl)furfur-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one (Formula KK-4)
 3-(α -cyclopropyl((5-(N-(N-cyano, methylthioimino)aminomethyl)furfur-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one (Formula KK-6)
 3-(α -cyclopropyl((5-(N-(N-cyano, N'-isopropylguanidine)aminomethyl)furfur-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one (Formula KK-7)

EXAMPLE 198

Refer to Chart LL.

3-(α -cyclopropyl((5-(N-benzylcarbamate)aminomethyl)furfur-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one (Formula LL-6)
 3-(α -cyclopropyl((5-aminomethyl)furfur-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one (Formula LL-7)

- EXAMPLE 199 Refer to Chart MM.
 3-(α -cyclopropyl((5-(N-benzylcarbamate)aminomethyl)thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one (Formula MM-6)
- 5 3-(α -cyclopropyl((5-aminomethyl)thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one (Formula MM-7)
 3-(α -cyclopropyl((5-(N-phenylsulphonyl)aminomethyl)thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one (Formula MM-8)
- 10 EXAMPLE 200 Refer to Chart NN.
 3-(α -cyclopropylfurfur-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one (Formula NN-5)
 3-(α -cyclopropyl(5-N-phenylsulphonyl)furfur-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one (Formula NN-7)
- 15 EXAMPLE 201 Refer to Chart OO.
 3-(α -cyclopropyl((5-methoxymethylhydroxymethylether)thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one (Formula OO-7)
 3-(α -cyclopropyl((5-hydroxymethyl)thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one (Formula OO-8)
- 20 EXAMPLE 202 Refer to Chart PP.
 3-(α -cyclopropyl((5-methoxymethyl)thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one (Formula PP-2)
 3-(α -cyclopropyl((5-azidomethyl)thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one (Formula PP-3)
- 25 3-(α -cyclopropyl((5-aminomethyl)thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one (Formula PP-4)
 3-(α -cyclopropyl((5-[N-acetyl]aminomethyl)thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one (Formula PP-5)
- 30 3-(α -cyclopropyl((5-[N-phenylsulphonyl]aminomethyl)thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one (Formula PP-6)
 3-(α -cyclopropyl((5-(4-carboethoxy-1,2,3-triazol-1-yl)methyl)thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one (Formula PP-7)
- 35 3-(α -cyclopropyl((5-(4-carboxylic-1,2,3-triazol-1-yl)methyl)thiophen-2-

- ylmethyl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one (prepared by hydrolyzing PP-7 to its corresponding carboxylic acid).
- EXAMPLE 203 3-(α -cyclopropyl((5-hydroxymethyl)thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one (Formula QQ-5) Refer to Chart QQ.
- 5 EXAMPLE 204 Refer to Chart RR.
- 3-(α -cyclopropyl((5-(N-(1-nitro-2-methylthioethen-2-ylmethyl)aminomethyl)thiophen-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one (Formula RR-3)
- 10 3-(α -cyclopropyl((5-(N-(1-nitro-2-[N-isopropyl])ethen-2-yl)aminomethyl)thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one (Formula RR-4)
- 3-(α -cyclopropyl((5-(N-(N-cyano, methylthioimino)aminomethyl)thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one (Formula RR-6)
- 15 3-(α -cyclopropyl((5-(N-(N-cyano, N'-isopropylguanidine)aminomethyl)thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one (Formula RR-7)
- EXAMPLE 205 Refer to Chart SS.
- 3-(α -cyclopropylthiophen-2-ylmethyl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one (Formula SS-5)
- 20 3-(α -cyclopropyl(5-N-phenylsulphonyl)thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one (Formula SS-7)
- EXAMPLE 206 Refer to Chart TT.
- 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(β -hydroxyphenethyl)-2H-pyran-2-one (Formula TT-2)
- 25 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(α -ethyl- β -hydroxyphenethyl)-2H-pyran-2-one (Formula TT-4)
- EXAMPLE 207 Refer to Chart UU.
- 3-(α [S]-Ethylbenzyl)-4-hydroxy-6-(α [R]-ethyl- β [S]-hydroxyphenethyl)-2H-pyran-2-one (Formula UU-6)
- 30 3-(α [S]-Ethylbenzyl)-4-hydroxy-6-(α [S]-ethyl- β [R]-hydroxyphenethyl)-2H-pyran-2-one (Formula UU-11)
- 3-(α [S]-Ethylbenzyl)-4-hydroxy-6-(α [R]-ethyl- β [R]-hydroxyphenethyl)-2H-pyran-2-one (Formula UU-13)
- 35 3-(α [S]-Ethylbenzyl)-4-hydroxy-6-(α [S]-ethyl- β [S]-hydroxyphenethyl)-2H-pyran-2-one (Formula UU-14)

The following compounds are diastereomers prepared from UU-16:

3-(α [R]-Ethylbenzyl)-4-hydroxy-6-(α [R]-ethyl- β [S]-hydroxyphenethyl)-
2H-pyran-2-one

3-(α [R]-Ethylbenzyl)-4-hydroxy-6-(α [S]-ethyl- β [R]-hydroxyphenethyl)-
2H-pyran-2-one

3-(α [R]-Ethylbenzyl)-4-hydroxy-6-(α [R]-ethyl- β [R]-hydroxyphenethyl)-
2H-pyran-2-one

3-(α [R]-Ethylbenzyl)-4-hydroxy-6-(α [S]-ethyl- β [S]-hydroxyphenethyl)-
2H-pyran-2-one

The following compounds are prepared by the procedures of Chart UU, but with UU-16 wherein the ethyl group is replaced with a cyclopropyl group:

3-(α [S]-Cyclopropylbenzyl)-4-hydroxy-6-(α [R]-ethyl- β [S]-
hydroxyphenethyl)-2H-pyran-2-one

3-(α [S]-Cyclopropylbenzyl)-4-hydroxy-6-(α [S]-ethyl- β [R]-
hydroxyphenethyl)-2H-pyran-2-one

3-(α [S]-Cyclopropylbenzyl)-4-hydroxy-6-(α [R]-ethyl- β [R]-
hydroxyphenethyl)-2H-pyran-2-one

3-(α [S]-Cyclopropylbenzyl)-4-hydroxy-6-(α [S]-ethyl- β [S]-
hydroxyphenethyl)-2H-pyran-2-one

3-(α [R]-Cyclopropylbenzyl)-4-hydroxy-6-(α [R]-ethyl- β [S]-
hydroxyphenethyl)-2H-pyran-2-one

3-(α [R]-Cyclopropylbenzyl)-4-hydroxy-6-(α [S]-ethyl- β [R]-
hydroxyphenethyl)-2H-pyran-2-one

3-(α [R]-Cyclopropylbenzyl)-4-hydroxy-6-(α [R]-ethyl- β [R]-
hydroxyphenethyl)-2H-pyran-2-one

3-(α [R]-Cyclopropylbenzyl)-4-hydroxy-6-(α [S]-ethyl- β [S]-
hydroxyphenethyl)-2H-pyran-2-one

EXAMPLE 208 3-(α -Ethylbenzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one: A
Four Week Oral Drug Safety and Toxicity Study in Beagle Dogs

Five groups of three (3) male and three (3) female young adult beagle dogs were given 3-(α -Ethylbenzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one in 95% ethyl alcohol orally in gelatin capsules at doses of 0 (95% ethyl alcohol vehicle control), 50, 100, 200 or 400 mg/kg/day for twenty-eight (28) consecutive days. Daily oral doses were divided into two (2) equal doses with at least seven (7) hours between the morning and afternoon dose. Parameters evaluated included twice daily clinical observations; daily evaluation of food and water consumption; twice weekly body weights; pretest and dosage day (dd) 15 or 16 and 24 or 25

electrocardiograms; pretest and dd 23 or 24 ophthalmology examinations; pretest and dd 1, 8, 14, 21 and 28 plasma drug levels; pretest and dd 8, 14, and 28 hemograms and serum chemistries; pretest and dd 14 and 28 urinalyses; terminal body weights, gross necropsy observations and absolute and relative organ weights; and histopathologic evaluation of organs and tissues.

Among other observations, daily oral doses of 50 to 400 mg/kg/day were associated with a dose related decrease in prostate size and weight. Table IV below shows that doses of 50 to 400 mg/kg/day, and particularly doses of 100 to 400 mg/kg/day, caused decreased prostate gland size and weight.

10 PREPARATION 52 5,6-Dihydro-4-hydroxy-6-(2-methylpropyl)-6-phenylethyl-2H-pyran-2-one (Formula AAA-1; R_1 = 2-methylpropyl, R_2 = phenylethyl) Refer to Chart AAA.

5-Methyl-1-phenyl-3-hexanone (4.0 g) is converted to the title compound using the general procedure for synthesis of 5,6-dihydropyrones of Preparation 16, A. to yield 4.0 g of the title compound as a white solid.

Physical characteristics are as follows:

MP 63-65 °C.

^1H NMR (300 MHz, CDCl_3): δ 0.98, 1.65, 1.83-1.91, 1.93-2.06, 2.66-2.75, 3.42, 7.14-7.32.

20 EXAMPLE 209 2H-Pyran-2-one, 3-diphenylmethyl-5,6-dihydro-4-hydroxy-6-(2-methylpropyl)-6-(2-phenylethyl)- (Formula AAA-3; R_1 = phenylethyl, R_2 = 2-methylpropyl) Refer to Chart AAA.

To a solution of 5,6-Dihydro-4-hydroxy-6-(2-methylpropyl)-6-phenylethyl-2H-pyran-2-one (150 mg) of Preparation 52 and benzhydrol (AAA-2) (202 mg) in dioxane, under Argon, is added [boron trifluoride etherate] (68 μL). The reaction mixture is stirred at room temperature for 12 hr. and then quenched with water. Ether is added and the combined organic layers are extracted with 0.1 N sodium hydroxide (3x 10 mL). The combined aqueous layers are cooled to 0°C and acidified to pH 1 using 2 N hydrochloric acid dropwise. The milky solution is extracted with methylene chloride (3x 15 mL) and the combined organic layers are washed with sat. sodium chloride, dried (sodium sulfate) and evaporated under reduced pressure to give the title compound as a light yellow foam.

Physical characteristics are as follows:

^1H NMR (300 MHz, CDCl_3): δ 0.94, 1.63-1.92, 1.97-2.22, 2.51-2.82, 5.77, 5.82, 7.10-7.39.

35 HRMS Found: 440.2351

EXAMPLE 210 2H-Pyran-2-one, 3-(1,3-diphenyl-2-propenyl)-5,6-dihydro-4-hydroxy-6-

(2-methylpropyl)-6-(2-phenylethyl)- (Formula WW-3; R_1 = phenylethyl, R_2 = 2-methylpropyl) Refer to Chart WW.

To a solution of 5,6-Dihydro-4-hydroxy-6-(2-methylpropyl)-6-phenylethyl-2H-pyran-2-one (250 mg) of Preparation 52 and 1,3-diphenyl allyl alcohol (WW-2) (383 mg) in dioxane, under Argon, is added [boron trifluoride etherate] (112 μ L). The reaction mixture is stirred at room temperature for 5 min. and then quenched with water. Ether is added and the combined organic layers are extracted with 0.1 N sodium hydroxide (3x 10 mL). The combined aqueous layers are cooled to 0°C and acidified to pH 1 using 2 N hydrochloric acid dropwise. The milky solution is extracted with methylene chloride (3x 15 mL) and the combined organic layers are washed with sat. sodium chloride, dried (sodium sulfate) and evaporated under reduced pressure to give the title compound as a white foam.

Physical characteristics are as follows:

^1H NMR complicated by presence of diastereomers.

^1H NMR (300 MHz, CDCl_3): δ 0.91-1.00, 1.57-2.19, 2.49-2.73, 5.25, 6.42-6.49, 6.63-6.71, 7.05-7.43.

HRMS Found: 467.2591

EXAMPLE 211 2H-Pyran-2-one, 3-(1,3-diphenyl-2-propyl)-5,6-dihydro-4-hydroxy-6-(2-methylpropyl)-6-(2-phenylethyl)- (Formula WW-4; R_1 = phenylethyl, R_2 = 2-methylpropyl) Refer to Chart WW.

3-(1,3-Diphenyl-2-propenyl)-5,6-dihydro-4-hydroxy-6-(2-methylpropyl)-6-(2-phenylethyl)-2H-pyran-2-one, of Example 210 (100 mg) is hydrogenated using the general procedure in Preparation 16, D, utilizing 10% Pd/C as catalyst, to yield 99 mg of the title compound as a white foam.

Physical characteristics are as follows:

^1H NMR complicated by presence of diastereomers.

^1H NMR (300 MHz, CDCl_3): δ 0.64-1.05, 1.52-2.18, 2.26-2.75, 4.37, 5.74, 6.95-7.48.

HRMS Found: 468.2664

Following procedures analogous to those described above and using starting materials and reagents readily known and available to one of ordinary skill in the art of organic synthesis, the following additional compounds of the present invention are prepared:

EXAMPLE 212 3-(α -Cyclopropyl-*meta*-[(phenylaminocarbonyl)amino]benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one

Physical characteristics are as follows:

FAB HRMS: 509.2451 (found).

EXAMPLE 213 3-(α -Cyclopropyl-*meta*-[(benzylaminocarbonyl)amino]benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one

Physical characteristics are as follows:

FAB HRMS: 523.2600 (found).

EXAMPLE 214 3-(α -Cyclopropyl-*meta*-[(4-methoxyphenylaminocarbonyl)amino]
benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one

5 Physical characteristics are as follows:

^1H NMR: δ 0.15, 0.38, 0.57, 0.76, 1.51, 1.78, 2.41, 2.69, 2.81, 3.26, 3.67, 5.69, 6.72,
6.9-7.4.

EXAMPLE 215 3-(α -Cyclopropyl-*meta*-[(4-bromophenylaminocarbonyl)amino] benzyl)-
6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one

10 Physical characteristics are as follows:

^1H NMR: δ 0.15, 0.36, 0.57, 0.76, 1.51, 1.70, 2.40, 2.65-2.85, 3.25, 5.71, 6.8-7.6.

EXAMPLE 216 3-(α -Cyclopropyl-*meta*-[(phenylsulfonylaminocarbonyl)amino] benzyl)-6-
(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one

Physical characteristics are as follows:

15 ^1H NMR: δ 0.11, 0.19, 0.40, 0.53, 0.81, 1.59, 1.81, 2.45, 2.7-2.85, 3.29, 5.7, 6.8-8.0.

EXAMPLE 217 2H-Pyran-2-one, 6-butyl-5,6-dihydro-3-(1,3-diphenyl-2-propenyl)-4-
hydroxy-6-phenylmethyl-

Physical characteristics are as follows:

EI-MS: (M+)=452

20 ^1H NMR: 0.8, 1.35, 1.6, 2.49, 2.98, 5.07, 6.5, 6.9, 7.1-7.4.

EXAMPLE 218 2H-Pyran-2-one, 6-butyl-5,6-dihydro-3-(1,3-diphenylpropyl)-4-hydroxy-
6-phenylmethyl-

Physical characteristics are as follows:

^1H NMR: 0.85, 1.1-1.3, 1.6, 2.3-2.6, 2.94, 4.23, 7.0-7.5.

25 EXAMPLE 219 2H-Pyran-2-one, 6-butyl-5,6-dihydro-4-hydroxy-6-phenylmethyl-3-(1-
phenyl-2-propenyl)-

Physical characteristics are as follows:

^1H NMR: 0.89, 1.1-1.7, 2.48, 3.0, 4.9-5.3, 6.3-6.6, 7.0-7.4.

EXAMPLE 220 2H-Pyran-2-one, 6-butyl-5,6-dihydro-4-hydroxy-6-phenylmethyl-3-(1-
phenylpropyl)-

30

Physical characteristics are as follows:

^1H NMR: 0.8-1.0, 1.2-1.7, 1.9-2.3, 2.45, 2.97, 4.05, 7.0-7.5.

EXAMPLE 221 3-(α -Cyclopropyl-*meta*-(*tert*-butoxycarbonyl-L-alanyl)amino)benzyl)-6-
(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one

35

Physical characteristics are as follows:

(M + Na)+ 583.2801.

EXAMPLE 222 3-(α -Cyclopropyl-*meta*-(N- α -*tert*-butoxycarbonyl-N-im-p-toluenesulfonyl-L-histidylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one

Physical characteristics are as follows:

5 (M + H)⁺ 781.3268.

EXAMPLE 223 3-(α -Cyclopropyl-*meta*-(4-bromophenylbenzoylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one

Physical characteristics are as follows:

M⁺ 571.1358.

10 EXAMPLE 224 3-(α -Cyclopropyl-*meta*-(4-chlorophenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one

Physical characteristics are as follows:

M⁺ 563.1528.

EXAMPLE 225 3-(α -Cyclopropyl-*meta*-(N-benzyloxycarbonyl-O- α -benzyl-L-glutamylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one

15

Physical characteristics are as follows:

(M + H)⁺ 743.3330.

EXAMPLE 226 3-(α -Cyclopropyl-*meta*-(N- α -*tert*-butoxycarbonyl-L-histidylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one

20

Physical characteristics are as follows:

(M + H)⁺ 627.3186.

EXAMPLE 227 3-(α -Cyclopropyl-*meta*-(4-cyanophenylbenzoylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one

Physical characteristics are as follows:

25 (M + H)⁺ 519.2277.

EXAMPLE 228 3-(α -Cyclopropyl-*meta*-(L-glutamylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one

EXAMPLE 229 3-(α -Cyclopropyl-*meta*-(8-quinolinesulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one

30

Physical characteristics are as follows:

M⁺ 580.

EXAMPLE 230 3-(α -Cyclopropyl-*meta*-(3-(1-indolyl)propanoylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one

Physical characteristics are as follows:

35 M⁺ 560.

EXAMPLE 231 3-(α -Cyclopropyl-*meta*-(2-pyridylacetyl-amino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one

Physical characteristics are as follows:

M+ 508.

5

EXAMPLE 232 2H-Pyran-2-one, 3-(α -cyclopropyl-[5-(methoxymethoxy-methyl)-thiophen-2-yl]-methyl)-5,6-dihydro-4-hydroxy-6-(2-methylpropyl)-6-(2-phenylethyl)-

Physical characteristics are as follows:

10 ^1H NMR (300 MHz, CDCl_3): δ 0.33, 0.46, 0.65, 0.92, 1.54-1.68, 1.70-1.84, 1.90-2.18, 3.37, 3.57, 4.65, 6.79, 6.86, 7.10-7.28.

HRMS Found: 423.2002.

EXAMPLE 233 2H-Pyran-2-one, 5,6-dihydro-4-hydroxy-6-(2-methylpropyl)-6-(2-phenylethyl)-3-(1-phenyl-2-propenyl)-

15 Physical characteristics are as follows:

^1H NMR complicated by presence of diastereomers.

^1H NMR (300 MHz, CDCl_3 , CD_3OD): δ 0.95-0.98, 1.60-1.71, 1.73-1.89, 1.90-2.14, 2.56-2.72, 3.46, 4.91, 5.11-5.20, 6.44-6.59, 7.11-7.33.

HRMS Found: 391.2273.

20 EXAMPLE 234 2H-Pyran-2-one, 5,6-dihydro-4-hydroxy-6-(2-methylpropyl)-6-(2-phenylethyl)-3-(1-phenylpropyl)-

Physical characteristics are as follows:

^1H NMR complicated by presence of diastereomers.

25 ^1H NMR (300 MHz, CDCl_3): δ 0.88-1.02, 1.54-2.36, 2.59, 3.36, 4.09, 7.03-7.28, 7.41-7.43.

HRMS Found: 393.2430.

EXAMPLE 235 2H-Pyran-2-one, 5,6-dihydro-3-diphenylmethyl-4-hydroxy-6,6-di-(2-phenylethyl)-

Physical characteristics are as follows:

30 ^1H NMR complicated by presence of diastereomers.

^1H NMR (300 MHz, CDCl_3): δ 2.09-2.24, 2.63-2.74, 5.79, 5.87, 7.10-7.35.

HRMS Found: 489.2430.

EXAMPLE 236 2H-Pyran-2-one, 5,6-dihydro-4-hydroxy-6,6-di-(2-phenylethyl)-3-(1,3-diphenyl-2-propenyl)-

35 Physical characteristics are as follows:

^1H NMR (300 MHz, CDCl_3): δ 2.03-2.27, 2.66-2.82, 5.24, 6.43, 6.68, 7.10-7.43.

HRMS Found: 515.2586.

EXAMPLE 237 2H-Pyran-2-one, 5,6-dihydro-4-hydroxy-6,6-di-(2-phenylethyl)-3-(1,3-diphenylpropyl)-

Physical characteristics are as follows:

5 ^1H NMR complicated by presence of diastereomers.

^1H NMR (300 MHz, CDCl_3): δ 1.52-1.91, 2.03-2.25, 2.31-2.78, 4.36, 5.96, 7.08-7.41.

HRMS Found: 517.2743.

EXAMPLE 238 2H-Pyran-2-one, 5,6-dihydro-4-hydroxy-3-(1,3-diphenyl-2-propenyl)-6-(3-phenylpropyl)-6-propyl-

10 Physical characteristics are as follows:

^1H NMR complicated by presence of diastereomers.

^1H NMR (300 MHz, CDCl_3): δ 0.84-0.93, 2.21-1.42, 1.56-1.85, 2.49-2.64, 5.17, 6.32-6.44, 6.48-6.66, 7.09-7.41.

EXAMPLE 239 2H-Pyran-2-one, 5,6-dihydro-4-hydroxy-3-(1,3-diphenylpropyl)-6-(3-phenylpropyl)-6-propyl-

15

Physical characteristics are as follows:

^1H NMR complicated by presence of diastereomers.

^1H NMR (300 MHz, CDCl_3): δ 0.79-1.05, 1.16-1.87, 2.23-2.74, 4.31, 5.64, 7.05-7.48.

EXAMPLE 240 2H-Pyran-2-one, 3-(α -cyclopropyl-[5-(methoxymethoxy-methyl)-thiophen-2-yl]-methyl)-5,6-dihydro-4-hydroxy-6-(2-phenylethyl)-6-propyl-

20

Physical characteristics are as follows:

^1H NMR complicated by presence of diastereomers.

25 ^1H NMR (300 MHz, CDCl_3): δ 0.38, 0.51, 0.72, 0.95, 1.37-1.51, 1.62-2.21, 2.44-2.58, 2.61-2.72, 3.39, 3.40, 3.80, 4.67, 6.51, 6.65, 6.88, 6.99, 7.16-7.30.

EXAMPLE 241 2H-Pyran-2-one, 3-(α -cyclopropyl-[5-(methoxymethoxy-methyl)-thiophen-2-yl]-methyl)-5,6-dihydro-4-hydroxy-6-(3-phenylpropyl)-6-propyl-

30

Physical characteristics are as follows:

^1H NMR complicated by presence of diastereomers.

^1H NMR (300 MHz, CDCl_3): δ 0.36-0.58, 0.71, 0.90, 1.23-1.42, 1.61-1.83, 2.47-2.62, 3.40, 3.43, 3.75, 4.68, 6.41, 6.86, 6.88, 6.92, 7.10-7.21, 7.26-7.32.

EXAMPLE 242 2H-Pyran-2-one, 5,6-dihydro-3-diphenylmethyl-4-hydroxy-6-(3-phenylpropyl)-6-propyl-

35

Physical characteristics are as follows:

^1H NMR (300 MHz, CDCl_3): δ 0.88, 1.22-1.38, 1.59-1.82, 2.48, 2.58, 5.71, 5.76, 7.07-

7.39.

EXAMPLE 243 3-(α -Cyclopropylbenzyl)-6-[1-cyclopropylmethyl-2-(tetrahydropyran-3-yl)ethyl]-4-hydroxy-2H-pyran-2-one

Physical characteristics are as follows:

5 ms: found m/z = 408.

EXAMPLE 244 3-(α -Cyclopropyl-*meta*-(ethylsulfonylamino)benzyl)-6-[1-cyclopropylmethyl-2-(tetrahydropyran-3-yl)ethyl]-4-hydroxy-2H-pyran-2-one

Physical characteristics are as follows:

10 ms: found m/z = 515.

EXAMPLE 245 3-(α -Cyclopropyl-*meta*-(4-methylphenylsulfonylamino)benzyl)-6-[1-cyclopropylmethyl-2-(tetrahydropyran-3-yl)ethyl]-4-hydroxy-2H-pyran-2-one

Physical characteristics are as follows:

15 ms: found m/z = 577.

EXAMPLE 246 3-(α -Cyclopropyl-*meta*-(4-methylphenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one

Physical characteristics are as follows:

ms: found m/z = 543.

20 EXAMPLE 247 3-(α -Cyclopropyl-*meta*-(ethylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one

Physical characteristics are as follows:

ms: found m/z = 481.

25 EXAMPLE 248 3-(α -Cyclopropyl-*meta*-(3-pyridylacetyl amino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one

Physical characteristics are as follows:

^1H NMR δ 0.22, 0.48, 0.64, 0.82, 1.60, 1.89, 2.48, 2.8, 2.9, 3.32, 5.69, 7.1, 7.2, 7.5, 7.8, 8.4, 8.5 ppm.

30 EXAMPLE 249 3-(α -Cyclopropyl-*meta*-(4-pyridylacetyl amino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one

Physical characteristics are as follows:

^1H NMR δ 0.22, 0.48, 0.64, 0.82, 1.6, 1.9, 2.5, 2.8, 2.9, 3.3, 5.71, 7.05, 7.2, 7.3, 7.5, 8.40 ppm.

35 PREPARATION 53 (4S,5R) 3-Butyryl-4-methyl-5-phenyl-2-oxazolidinone (Formula W-1)
Refer to Chart W.

(4S,5R) 4-Methyl-5-phenyl-2-oxazolidinone (10.0 g) is added to tetrahydrofuran (115

mL) and cooled to -78°C . To that solution is added n-butyl lithium (38.8 mL, 1.6 M in hexane) and the resulting reaction stirred at -78°C for 1 hour. To that solution is added butyryl chloride (6.75 mL) and the reaction stirred for an additional 1.5 hours. The reaction is warmed to room temperature and quenched via addition of water (100 mL). The reaction is extracted with ethyl acetate, dried (sodium sulfate) and solvent removed in vacuo to yield the crude product. The residue is dissolved in hexane and placed in the freezer overnight. Two crops of crystals are obtained (8.5 g, 4.5 g) to yield a total of 13.0 grams of the title product.

PREPARATION 54 (4S,5R) 3-(α [R]-Benzyl)butyryl-4-methyl-5-phenyl-2-oxazolidinone (Formula W-3) Refer to Chart W.

(4S,5R) 3-Butyryl-4-methyl-5-phenyl-2-oxazolidinone of Preparation 53 (4.0 g) is cooled to -78°C in tetrahydrofuran (54 mL) under a nitrogen atmosphere. Lithium diisopropylamide (LDA, 2.0 M) is added dropwise over several minutes and stirring continued for 30 minutes. The reaction temperature is then adjusted to 0°C and benzyl bromide (2.15 mL) is added. The reaction is then allowed to warm to room temperature and after 30 minutes at room temperature, water (150 mL) is added and the reaction is extracted with ethyl acetate. The combined ethyl acetate extracts are dried and solvent removed in vacuo to yield a pale yellow oil. The oil is dissolved in toluene and applied to a silica gel column eluting with hexane to yield 4.4 g of the desired title product as an oil. $[\alpha]_D = -69^{\circ}$.

PREPARATION 55 (R) α -ethyl hydrocinnamic acid (Formula W-4) Refer to Chart W.

(4S,5R) 3-(α [R]-Benzyl)butyryl-4-methyl-5-phenyl-2-oxazolidinone of Preparation 54 (3.48 g) is added to a 3:1 mixture of tetrahydrofuran/water (35 mL). To that solution is added a lithium hydroxide/hydrogen peroxide solution (from 10.3 mL of a @ 10 M solution of hydrogen peroxide and 911 mg of lithium hydroxide monohydrate) and the resulting solution stirred for 3 hours. Water (50 mL) is added and the reaction is then extracted with ethyl acetate. The aqueous is acidified with 2N hydrochloric acid and extracted with methylene chloride to yield 1.71 g of pure title product as a colorless liquid. $[\alpha]_D = -36^{\circ}$.

PREPARATION 56 (R) 2,2-Dimethyl-6-(α -ethylphenethyl)-4H-1,3-dioxin-4-one (Formula W-7) Refer to Chart W.

(R) α -Ethyl hydrocinnamic acid of Preparation 55 (1.58 g) is added to methylene chloride (5 mL) followed by the addition of oxalyl chloride (0.82 mL, 1.05 equiv) at room temperature. After stirring for 4 hours, the solvent and excess oxalyl chloride is removed via evaporation to yield W-8.

tert-Butyl acetate (2.4 mL, 17.8 mmol) is added to a tetrahydrofuran solution (10 mL) of lithium diisopropylamide (8.9 mL, 2.0 M LDA) dropwise at -78°C . After stirring for 30 minutes, this lithium enolate (W-9) is added to the above acid chloride (W-8) (in tetrahydrofuran (5 mL)) dropwise via cannular at -78°C . After 20 minutes at -78°C , water (5 mL) is added and

-125-

the reaction warmed to 0°C. 1N Hydrochloric acid (10 mL) is added slowly at 0°C followed by ethyl acetate (20 mL). The organic layer is separated and the aqueous extracted with several addition times with ethyl acetate. The combined extracts are dried and solvent removed in vacuo to yield 3.00 g of tert-butyl 5-phenyl-4[R]-ethyl-3-oxo-pentanoate (W-10). Sulfuric acid (0.44 mL) is added dropwise to a mixture of tert-butyl 5-phenyl-4[R]-ethyl-3-oxo-pentanoate (3.0 g), acetone (1.5 mL) and acetic anhydride (3 mL) with stirring at 0°C overnight. The reaction is then poured into saturated sodium bicarbonate (50 mL) and ice. The mixture is stirred and warmed to room temperature for 30 minutes and then extracted with ether (2 X 30 mL). The combined ether extracts are dried over magnesium sulfate and solvent removed in vacuo to yield 2.81 g of crude title product. Silica gel chromatography (acetone/ethyl acetate/hexane; 1:3:16) affords 2.10 g of the desired product as a colorless oil.

Physical characteristics are as follows:

H-NMR: 0.92(m), 1.60(s), 1.61(s), 2.41(m), 2.77, 2.80, 5.13, 7.12-7.27.

EXAMPLE 250 (3S,6R) 3-(α -ethylbenzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one (Formula CC-5) Refer to Chart CC.

To (R) 3-phenylvaleric acid (CC-1) (Chemistry Letters (1981) 913-16) (400 mg) in anhydrous methylene chloride (5 mL) is added oxalyl chloride (0.21 mL) and the resulting solution heated at reflux for 2 hours. The reaction is then cooled to room temperature and the solvent and excess oxalyl chloride removed in vacuo to yield the crude acid chloride (CC-2). The acid chloride is dissolved in toluene (10 mL) and then heated to reflux. To that solution, at reflux, is added a mixture of triethylamine (202 mg) and (R) 2,2-dimethyl-6-(α -ethylphenethyl)-4H-1,3-dioxin-4-one (350 mg) (CC-3) in toluene (1.5 mL) dropwise. A long needle is inserted via rubber septa just above the solvent to sweep acetone from the reaction. The reaction is maintained at reflux for 2.5 hours. The reaction is cooled to room temperature and the triethylamine hydrochloride is removed via filtration. The filtrate is evaporated in vacuo and the residue, containing CC-4, is added to a methanol/water mixture (6:1; 35 mL) and 0.5 g of sodium carbonate added and the reaction stirred at room temperature overnight. The methanol is removed in vacuo and a saturated sodium carbonate solution (20 mL) added to the crude reaction mixture. That material is extracted with hexane (2 X 20 mL) which contains the methyl ester (R) α -ethyl hydrocinnamic acid (CC-6). The aqueous layer is made acidic by adding 1N hydrochloric acid at 0°C to a pH @ 3. That aqueous is extracted with ethyl acetate (2 X 30 mL), dried (sodium sulfate) and solvent removed in vacuo to yield 359 mg of crude title product. Chromatography (silica gel; 15% ethyl acetate/methylene chloride) affords 299.9 mg of material which is recrystallized to yield 210.0 mg of product. An additional 20 mg of product is recovered from the mother liquors to yield a total of 230.0 mg of the title product.

Physical characteristics are as follows:

MP 141-2°C.

PREPARATION 57 (4R,5S) 3-Butyryl-4-methyl-5-phenyl-2-oxazolidinone (Formula X-1)

Refer to Chart X.

(4R,5S) 4-Methyl-5-phenyl-2-oxazolidinone (10.0 g) is added to tetrahydrofuran (115 mL) and cooled to -78°C. To that solution is added n-butyl lithium (38.8 mL, 1.6 M in hexane) and the resulting reaction stirred at -78°C for 1 hour. To that solution is added butyryl chloride (6.75 mL) and the reaction stirred for an additional 1.5 hours. The reaction is warmed to room temperature and quenched via addition of water (100 mL). The reaction is extracted with ethyl acetate, dried (sodium sulfate) and solvent removed in vacuo to yield the crude title product (X-1). The residue is dissolved in hexane and placed in the freezer overnight. Two crops of crystals are obtained (11.5 g, 1.7 g) to yield a total of 13.2 grams of product.

Physical characteristics are as follows:

H-NMR (CDCl₃) 0.88, 0.91, 0.98, 1.00, 1.03, 1.68, 1.70, 1.73, 1.75, 2.88, 2.91, 2.92, 2.93, 2.95, 2.97, 4.74, 4.77, 4.79, 4.74, 4.77, 4.79, 5.66, 5.68, 7.26-42.

15 PREPARATION 58 (4R,5S) 3-(α [S]-Benzyl)butyryl-4-methyl-5-phenyl-2-oxazolidinone (Formula X-3) Refer to Chart X.

(4R,5S) 3-Butyryl-4-methyl-5-phenyl-2-oxazolidinone of Preparation 57 (11.5g) is cooled to -78°C in tetrahydrofuran (100 mL) under a nitrogen atmosphere. Lithium diisopropylamide (LDA, prepared from 33.5 mL of 1.6 M n-butyl lithium and 7.83 mL of diisopropylamine; total volume of tetrahydrofuran is 80 mL) is added dropwise over several minutes and stirring continued for 30 minutes. The reaction temperature is then adjusted to 0°C and benzyl bromide (8.3 mL) is added. The reaction is then allowed to warm to room temperature and after 30 minutes at room temperature the reaction is quenched with 0.25 M hydrochloric acid. The reaction is extracted with ethyl acetate (3 X 100 mL). The combined ethyl acetate extracts are dried and solvent removed in vacuo to yield a pale yellow oil. The oil is dissolved in toluene and applied to a silica gel column, eluting with hexane (500 mL) and then 15% ethyl acetate/hexane to yield 13.8 g of the desired title product as an oil.

Physical characteristics are as follows:

30 H-NMR (CDCl₃) 0.619, 0.641, 0.024, 0.949, 0.973, 1.56, 1.58, 1.60, 1.62, 1.72, 1.75, 1.78, 1.80, 2.74, 2.76, 2.79, 2.81, 2.97, 2.99, 3.01, 3.04, 4.16, 4.16, 4.20, 4.71, 4.74, 4.76, 5.59, 5.61, 7.16-7.42.

PREPARATION 59 (S) α -ethyl hydrocinnamic acid (Formula X-4) Refer to Chart X.

(4R,5S) 3-(α [S]-Benzyl)butyryl-4-methyl-5-phenyl-2-oxazolidinone of Preparation 58 (1.50 g) is added to a 3:1 mixture of tetrahydrofuran/water (15 mL). To that solution is added a lithium hydroxide/hydrogen peroxide solution (from 4.45 mL of an @ 10 M solution of hydrogen peroxide and 393 mg of lithium hydroxide monohydrate) and the resulting solution

-127-

stirred for 3 hours. Water (50 mL) is added and the reaction is then extracted with ethyl acetate. The aqueous is acidified with 2N hydrochloric acid and extracted with methylene chloride to yield 0.746 g of pure title product as a colorless liquid. $[\alpha]_D = +34^\circ$.

PREPARATION 60 (S) 2,2-Dimethyl-6-(α -ethylphenethyl)-4H-1,3-dioxin-4-one (Formula X-

5 7) Refer to Chart X.

Following the procedure described for the preparation of (R) 2,2-dimethyl-6-(α -ethylphenethyl)-4H-1,3-dioxin-4-one of Preparation 56, 6.5 grams of the title product is prepared.

Physical characteristics are as follows:

10 H-NMR: 0.92(m), 1.60(s), 1.16(s), 2.41(m), 2.77, 2.80, 5.13, 7.12-7.27.

EXAMPLE 251 (3S,6S) 3-(α -ethylbenzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one (Formula DD-5) Refer to Chart DD.

Following the procedure described for the preparation of (3S,6R) 3-(α -ethylbenzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one of Example 250, 1.40 grams of the title product is
15 prepared.

Physical characteristics are as follows:

MP 162-164°C.

EXAMPLE 252 Sodium (3S,6R) 3-(α -ethylbenzyl)-6-(α -ethylphenethyl)-2H-pyran-2-one
4-oxide

20 (3S,6R) 3-(α -ethylbenzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one of Example 250 (36.2 mg) is added to 1.0 mL of tetrahydrofuran. To that solution is added 0.4 mL of 0.25 N sodium hydroxide at room temperature. That mixture is stirred for 30 minutes and the tetrahydrofuran and water are removed in vacuo. The resulting salt is washed with ethyl ether and dried in the vacuum oven over night. This affords 37.5 mg of the desired sodium salt, title
25 product.

Physical characteristics are as follows:

MP 210°C (decomposes).

30 H-NMR (DMSO-d₆) 0.739 (multiplet), 0.758 (multiplet), 1.431 (multiplet), 1.896 (multiplet), 2.298 (multiplet), 2.658 (part of an ABX), 2.759 (part of an ABX), 3.982 (triplet), 5.199 (singlet), 6.99-7.37 (multiplet).

EXAMPLE 253 (3R,6R) 3-(α -ethylbenzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one (Formula AA-5) Refer to Chart AA.

Physical characteristics are as follows:

MP 161-3°C.

35 EXAMPLE 254 (3R,6S) 3-(α -ethylbenzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one (Formula BB-5) Refer to Chart BB.

Physical characteristics are as follows:

H-NMR: 0.83 (m), 0.95 (m), 1.62 (m), 2.13 (m), 2.49 (m), 2.80 (m), 2.88 (m), 4.26 (m), 5.7 (s), 7.02-7.43 (m).

Utilizing procedures described above, or analogous thereto, the following additional

5 compounds of the present invention are prepared:

3-(α -Ethyl(furfur-2-yl)) Series

C-6 aryls with ethyl and cyclopropylmethyl:

3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one

3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(α -ethyl-[p-fluorophenethyl])-2H-pyran-2-one

10 3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(α -ethyl-[p-chlorophenethyl])-2H-pyran-2-one

3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(α -ethyl-[p-bromophenethyl])-2H-pyran-2-one

3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(α -ethyl-[p-methylphenethyl])-2H-pyran-2-one

3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(α -ethyl-[p-methoxyphenethyl])-2H-pyran-2-one

3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(α -ethyl-[p-hydroxyphenethyl])-2H-pyran-2-one

15 3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(α -ethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-one

3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(α -ethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-one

3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-fluorophenethyl])-2H-pyran-2-one

3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-chlorophenethyl])-2H-pyran-2-one

3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-bromophenethyl])-2H-pyran-2-one

20 3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-methylphenethyl])-2H-pyran-2-one

3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-methoxyphenethyl])-2H-pyran-2-one

3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-hydroxyphenethyl])-2H-pyran-2-one

25 3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-one

3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-one

C-6 tetrahydrofuryl:

30 3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(1-(tetrahydrofuran-2-ylmethyl)propyl)-2H-pyran-2-one

3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(1-(tetrahydrofuran-3-ylmethyl)propyl)-2H-pyran-2-one

3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(1-(tetrahydrofuran-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one

3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(1-(tetrahydrofuran-3-ylmethyl)cyclopropylmethyl)-2H-

35 pyran-2-one

C-6 tetrahydropyran:

- 3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(1-(tetrahydropyran-2-ylmethyl)propyl)-2H-pyran-2-one
 3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(1-(tetrahydropyran-3-ylmethyl)propyl)-2H-pyran-2-one
 3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(1-(tetrahydropyran-4-ylmethyl)propyl)-2H-pyran-2-one
 3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(1-(tetrahydropyran-2-ylmethyl)cyclopropylmethyl)-2H-
 5 pyran-2-one
 3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(1-(tetrahydropyran-3-ylmethyl)cyclopropylmethyl)-2H-
 pyran-2-one
 3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(1-(tetrahydropyran-4-ylmethyl)cyclopropylmethyl)-2H-
 pyran-2-one
- 10 C-6 furans/thiophenes:
 3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(1-(furan-2-ylmethyl)propyl)-2H-pyran-2-one
 3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(1-(furan-3-ylmethyl)propyl)-2H-pyran-2-one
 3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(1-(thiophen-2-ylmethyl)propyl)-2H-pyran-2-one
 3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(1-(thiophen-3-ylmethyl)propyl)-2H-pyran-2-one
- 15 3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(1-(furan-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one
 3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(1-(furan-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one
 3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(1-(thiophen-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one
 3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(1-(thiophen-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one
 3-(α -Cyclopropyl(furfur-2-yl)) Series
- 20 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one
 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(α -ethyl-[p-fluorophenethyl])-2H-pyran-2-one
 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(α -ethyl-[p-chlorophenethyl])-2H-pyran-2-one
 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(α -ethyl-[p-bromophenethyl])-2H-pyran-2-one
 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(α -ethyl-[p-methylphenethyl])-2H-pyran-2-one
- 25 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(α -ethyl-[p-methoxyphenethyl])-2H-pyran-2-one
 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(α -ethyl-[p-hydroxyphenethyl])-2H-pyran-2-one
 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(α -ethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-
 one
 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(α -ethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-
 30 one
 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-fluorophenethyl])-2H-pyran-
 2-one
 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-chlorophenethyl])-2H-pyran-
 2-one
 35 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-bromophenethyl])-2H-
 pyran-2-one

- 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-methylphenethyl])-2H-pyran-2-one
- 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-methoxyphenethyl])-2H-pyran-2-one
- 5 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-hydroxyphenethyl])-2H-pyran-2-one
- 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-one
- 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-one
- 10 2H-pyran-2-one
- C-6 tetrahydrofuryl:
- 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(1-(tetrahydrofuran-2-ylmethyl)propyl)-2H-pyran-2-one
- 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(1-(tetrahydrofuran-3-ylmethyl)propyl)-2H-pyran-2-one
- 15 one
- 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(1-(tetrahydrofuran-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one
- 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(1-(tetrahydrofuran-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one
- 20 C-6 tetrahydropyran:
- 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(1-(tetrahydropyran-2-ylmethyl)propyl)-2H-pyran-2-one
- 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(1-(tetrahydropyran-3-ylmethyl)propyl)-2H-pyran-2-one
- 25 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(1-(tetrahydropyran-4-ylmethyl)propyl)-2H-pyran-2-one
- 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(1-(tetrahydropyran-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one
- 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(1-(tetrahydropyran-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one
- 30 2H-pyran-2-one
- 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(1-(tetrahydropyran-4-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one
- C-6 furans/thiophenes:
- 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(1-(furan-2-ylmethyl)propyl)-2H-pyran-2-one
- 35 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(1-(furan-3-ylmethyl)propyl)-2H-pyran-2-one
- 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(1-(thiophen-2-ylmethyl)propyl)-2H-pyran-2-one

- 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(1-(thiophen-3-ylmethyl)propyl)-2H-pyran-2-one
- 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(1-(furan-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one
- 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(1-(furan-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one
- 5 one
- 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(1-(thiophen-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one
- 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(1-(thiophen-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one
- 10 3-(α -Ethyl(5-methyl(furfur-2-yl))) Series
- C-6 aryls with ethyl and cyclopropylmethyl:
- 3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one
- 3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -ethyl-[p-fluorophenethyl])-2H-pyran-2-one
- 3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -ethyl-[p-chlorophenethyl])-2H-pyran-2-one
- 15 3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -ethyl-[p-bromophenethyl])-2H-pyran-2-one
- 3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -ethyl-[p-methylphenethyl])-2H-pyran-2-one
- 3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -ethyl-[p-methoxyphenethyl])-2H-pyran-2-one
- 3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -ethyl-[p-hydroxyphenethyl])-2H-pyran-2-one
- 3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -ethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-one
- 20 2-one
- 3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -ethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-one
- 3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-fluorophenethyl])-2H-pyran-2-one
- 25 3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-chlorophenethyl])-2H-pyran-2-one
- 3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-bromophenethyl])-2H-pyran-2-one
- 3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-methylphenethyl])-2H-pyran-2-one
- 30 3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-methoxyphenethyl])-2H-pyran-2-one
- 3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-hydroxyphenethyl])-2H-pyran-2-one
- 35 3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-one

3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -cyclopropylmethyl-(p-trifluoromethylphenethyl))-2H-pyran-2-one

C-6 tetrahydrofuryl:

3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(tetrahydrofuran-2-ylmethyl)propyl)-2H-pyran-2-one

3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(tetrahydrofuran-3-ylmethyl)propyl)-2H-pyran-2-one

3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(tetrahydrofuran-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one

3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(tetrahydrofuran-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one

C-6 tetrahydropyran:

3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(tetrahydropyran-2-ylmethyl)propyl)-2H-pyran-2-one

3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(tetrahydropyran-3-ylmethyl)propyl)-2H-pyran-2-one

3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(tetrahydropyran-4-ylmethyl)propyl)-2H-pyran-2-one

3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(tetrahydropyran-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one

3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(tetrahydropyran-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one

3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(tetrahydropyran-4-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one

C-6 furans/thiophenes:

3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(furan-2-ylmethyl)propyl)-2H-pyran-2-one

3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(furan-3-ylmethyl)propyl)-2H-pyran-2-one

3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(thiophen-2-ylmethyl)propyl)-2H-pyran-2-one

3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(thiophen-3-ylmethyl)propyl)-2H-pyran-2-one

3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(furan-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one

3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(furan-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one

3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(thiophen-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one

35

3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(thiophen-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one

pyran-2-one

3-(α -Cyclopropyl(5-methyl(furfur-2-yl))) Series

3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one

3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -ethyl-[p-fluorophenethyl])-2H-pyran-2-

5 one

3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -ethyl-[p-chlorophenethyl])-2H-pyran-2-one

3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -ethyl-[p-bromophenethyl])-2H-pyran-2-one

10 3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -ethyl-[p-methylphenethyl])-2H-pyran-2-one

3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -ethyl-[p-methoxyphenethyl])-2H-pyran-2-one

3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -ethyl-[p-hydroxyphenethyl])-2H-pyran-

15 2-one

3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -ethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-one

3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -ethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-one

20 3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-fluorophenethyl])-2H-pyran-2-one

3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-chlorophenethyl])-2H-pyran-2-one

3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-bromophenethyl])-2H-pyran-2-one

25 bromophenethyl])-2H-pyran-2-one

3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-methylphenethyl])-2H-pyran-2-one

3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-methoxyphenethyl])-2H-pyran-2-one

30 3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-hydroxyphenethyl])-2H-pyran-2-one

3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-one

3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-one

35 trifluoromethylphenethyl])-2H-pyran-2-one

C-6 tetrahydrofuryl:

- 3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(tetrahydrofuran-2-ylmethyl)propyl)-2H-pyran-2-one
- 3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(tetrahydrofuran-3-ylmethyl)propyl)-2H-pyran-2-one
- 5 3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(tetrahydrofuran-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one
- 3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(tetrahydrofuran-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one
- C-6 tetrahydropyran:
- 10 3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(tetrahydropyran-2-ylmethyl)propyl)-2H-pyran-2-one
- 3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(tetrahydropyran-3-ylmethyl)propyl)-2H-pyran-2-one
- 3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(tetrahydropyran-4-ylmethyl)propyl)-2H-pyran-2-one
- 15 3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(tetrahydropyran-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one
- 3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(tetrahydropyran-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one
- 20 3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(tetrahydropyran-4-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one
- C-6 furans/thiophenes:
- 3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(furan-2-ylmethyl)propyl)-2H-pyran-2-one
- 25 3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(furan-3-ylmethyl)propyl)-2H-pyran-2-one
- 3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(thiophen-2-ylmethyl)propyl)-2H-pyran-2-one
- 3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(thiophen-3-ylmethyl)propyl)-2H-pyran-2-one
- 30 3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(furan-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one
- 3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(furan-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one
- 35 3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(thiophen-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one

3-(α -cyclopropyl(5-methyl(furfur-2-yl)))-4-hydroxy-6-(1-(thiophen-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one

3-(α -Ethyl(thiophen-2-ylmethyl)) Series

C-6 aryls with ethyl and cyclopropylmethyl:

- 5 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one
- 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethyl-[p-fluorophenethyl])-2H-pyran-2-one
- 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethyl-[p-chlorophenethyl])-2H-pyran-2-one
- 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethyl-[p-bromophenethyl])-2H-pyran-2-one
- 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethyl-[p-methylphenethyl])-2H-pyran-2-one
- 10 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethyl-[p-methoxyphenethyl])-2H-pyran-2-one
- 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethyl-[p-hydroxyphenethyl])-2H-pyran-2-one
- 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-one
- 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-one
- 15 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-fluorophenethyl])-2H-pyran-2-one
- 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-chlorophenethyl])-2H-pyran-2-one
- 20 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-bromophenethyl])-2H-pyran-2-one
- 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-methylphenethyl])-2H-pyran-2-one
- 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-methoxyphenethyl])-2H-pyran-2-one
- 25 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-hydroxyphenethyl])-2H-pyran-2-one
- 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-one
- 30 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-one
- C-6 tetrahydrofuryl:
- 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(tetrahydrofuran-2-ylmethyl)propyl)-2H-pyran-2-one
- 35 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(tetrahydrofuran-3-ylmethyl)propyl)-2H-pyran-2-one

- 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(tetrahydrofuran-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one
- 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(tetrahydrofuran-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one
- 5 C-6 tetrahydropyran:
- 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(tetrahydropyran-2-ylmethyl)propyl)-2H-pyran-2-one
- 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(tetrahydropyran-3-ylmethyl)propyl)-2H-pyran-2-one
- 10 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(tetrahydropyran-4-ylmethyl)propyl)-2H-pyran-2-one
- 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(tetrahydropyran-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one
- 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(tetrahydropyran-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one
- 15 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(tetrahydropyran-4-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one
- C-6 furans/thiophenes:
- 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(furan-2-ylmethyl)propyl)-2H-pyran-2-one
- 20 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(furan-3-ylmethyl)propyl)-2H-pyran-2-one
- 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(thiophen-2-ylmethyl)propyl)-2H-pyran-2-one
- 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(thiophen-3-ylmethyl)propyl)-2H-pyran-2-one
- 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(furan-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one
- 25 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(furan-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one
- 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(thiophen-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one
- 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(thiophen-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one
- 30 α -Cyclopropyl(thiophen-2-ylmethyl) Series
- 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one
- 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethyl-[p-fluorophenethyl])-2H-pyran-2-one
- 35 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethyl-[p-chlorophenethyl])-2H-pyran-2-one

- 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethyl-[p-bromophenethyl])-2H-pyran-2-one
- 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethyl-[p-methylphenethyl])-2H-pyran-2-one
- 5 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethyl-[p-methoxyphenethyl])-2H-pyran-2-one
- 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethyl-[p-hydroxyphenethyl])-2H-pyran-2-one
- 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-one
- 10 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-one
- 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-fluorophenethyl])-2H-pyran-2-one
- 15 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-chlorophenethyl])-2H-pyran-2-one
- 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-bromophenethyl])-2H-pyran-2-one
- 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-methylphenethyl])-2H-pyran-2-one
- 20 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-methoxyphenethyl])-2H-pyran-2-one
- 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-hydroxyphenethyl])-2H-pyran-2-one
- 25 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-one
- 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-one
- C-6 tetrahydrofuryl:
- 30 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(tetrahydrofuran-2-ylmethyl)propyl)-2H-pyran-2-one
- 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(tetrahydrofuran-3-ylmethyl)propyl)-2H-pyran-2-one
- 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(tetrahydrofuran-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one
- 35 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(tetrahydrofuran-3-

- ylmethyl)cyclopropylmethyl)-2H-pyran-2-one
 C-6 tetrahydropyran:
 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(tetrahydropyran-2-ylmethyl)propyl)-2H-pyran-2-one
 5 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(tetrahydropyran-3-ylmethyl)propyl)-2H-pyran-2-one
 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(tetrahydropyran-4-ylmethyl)propyl)-2H-pyran-2-one
 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(tetrahydropyran-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one
 10 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(tetrahydropyran-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one
 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(tetrahydropyran-4-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one
 15 C-6 furans/thiophenes:
 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(furan-2-ylmethyl)propyl)-2H-pyran-2-one
 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(furan-3-ylmethyl)propyl)-2H-pyran-2-one
 20 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(thiophen-2-ylmethyl)propyl)-2H-pyran-2-one
 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(thiophen-3-ylmethyl)propyl)-2H-pyran-2-one
 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(furan-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one
 25 2H-pyran-2-one
 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(furan-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one
 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(thiophen-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one
 30 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(thiophen-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one
 3-(α -Ethyl(5-methyl(thiophen-2-ylmethyl))) Series
 C-6 aryls with ethyl and cyclopropylmethyl:
 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one
 35 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(α -ethyl-[p-fluorophenethyl])-2H-pyran-2-one

- 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(α -ethyl-[p-chlorophenethyl])-2H-pyran-2-one
- 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(α -ethyl-[p-bromophenethyl])-2H-pyran-2-one
- 5 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(α -ethyl-[p-methylphenethyl])-2H-pyran-2-one
- 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(α -ethyl-[p-methoxyphenethyl])-2H-pyran-2-one
- 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(α -ethyl-[p-hydroxyphenethyl])-2H-pyran-2-one
- 10 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(α -ethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-one
- 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(α -ethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-one
- 15 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-fluorophenethyl])-2H-pyran-2-one
- 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-chlorophenethyl])-2H-pyran-2-one
- 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-bromophenethyl])-2H-pyran-2-one
- 20 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-methylphenethyl])-2H-pyran-2-one
- 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-methoxyphenethyl])-2H-pyran-2-one
- 25 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-hydroxyphenethyl])-2H-pyran-2-one
- 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-one
- 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-one
- 30 C-6 tetrahydrofuryl:
- 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(tetrahydrofuran-2-ylmethyl)propyl)-2H-pyran-2-one
- 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(tetrahydrofuran-3-ylmethyl)propyl)-2H-pyran-2-one
- 35 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(tetrahydrofuran-2-

ylmethyl)cyclopropylmethyl)-2H-pyran-2-one

3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(tetrahydrofuran-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one

C-6 tetrahydropyran:

5 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(tetrahydropyran-2-ylmethyl)propyl)-2H-pyran-2-one

3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(tetrahydropyran-3-ylmethyl)propyl)-2H-pyran-2-one

3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(tetrahydropyran-4-ylmethyl)propyl)-2H-pyran-2-one

10 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(tetrahydropyran-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one

3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(tetrahydropyran-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one

15 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(tetrahydropyran-4-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one

C-6 furans/thiophenes:

3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(furan-2-ylmethyl)propyl)-2H-pyran-2-one

20 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(furan-3-ylmethyl)propyl)-2H-pyran-2-one

3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(thiophen-2-ylmethyl)propyl)-2H-pyran-2-one

3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(thiophen-3-ylmethyl)propyl)-2H-pyran-2-one

25 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(furan-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one

3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(furan-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one

30 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(thiophen-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one

3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(thiophen-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one

3-(α -Cyclopropyl(5-methyl(thiophen-2-ylmethyl))) Series

35 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one

-141-

- 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(α -ethyl-[p-fluorophenethyl])-2H-pyran-2-one
- 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(α -ethyl-[p-chlorophenethyl])-2H-pyran-2-one
- 5 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(α -ethyl-[p-bromophenethyl])-2H-pyran-2-one
- 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(α -ethyl-[p-methylphenethyl])-2H-pyran-2-one
- 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(α -ethyl-[p-methoxyphenethyl])-2H-pyran-2-one
- 10 2H-pyran-2-one
- 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(α -ethyl-[p-hydroxyphenethyl])-2H-pyran-2-one
- 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(α -ethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-one
- 15 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(α -ethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-one
- 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-fluorophenethyl])-2H-pyran-2-one
- 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-chlorophenethyl])-2H-pyran-2-one
- 20 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-bromophenethyl])-2H-pyran-2-one
- 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-methylphenethyl])-2H-pyran-2-one
- 25 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-methoxyphenethyl])-2H-pyran-2-one
- 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-hydroxyphenethyl])-2H-pyran-2-one
- 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-one
- 30 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-one
- C-6 tetrahydrofuryl:
- 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(tetrahydrofuran-2-ylmethyl)propyl)-2H-pyran-2-one
- 35 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(tetrahydrofuran-3-

- ylmethyl)propyl)-2H-pyran-2-one
 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(tetrahydrofuran-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one
 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(tetrahydrofuran-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one
 5 ylmethyl)cyclopropylmethyl)-2H-pyran-2-one
 C-6 tetrahydropyran:
 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(tetrahydropyran-2-ylmethyl)propyl)-2H-pyran-2-one
 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(tetrahydropyran-3-ylmethyl)propyl)-2H-pyran-2-one
 10 ylmethyl)propyl)-2H-pyran-2-one
 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(tetrahydropyran-4-ylmethyl)propyl)-2H-pyran-2-one
 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(tetrahydropyran-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one
 15 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(tetrahydropyran-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one
 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(tetrahydropyran-4-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one
 C-6 furans/thiophenes:
 20 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(furan-2-ylmethyl)propyl)-2H-pyran-2-one
 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(furan-3-ylmethyl)propyl)-2H-pyran-2-one
 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(thiophen-2-ylmethyl)propyl)-2H-pyran-2-one
 25 2H-pyran-2-one
 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(thiophen-3-ylmethyl)propyl)-2H-pyran-2-one
 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(furan-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one
 30 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(furan-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one
 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(thiophen-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one
 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(thiophen-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one
 35 ylmethyl)cyclopropylmethyl)-2H-pyran-2-one
 Sulphonamides Cyclopropyl series

2-propyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]furfur-2-yl]-
 1-ethyl-
 2-propyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-
 sulfonamide
 2-propyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]furfur-2-yl]-p-
 nitrobenzamide
 2-propyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-
 phenylsulfonamide
 2-propyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]furfur-2-yl]-p-
 nitrobenzamide
 2-propyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-
 phenylsulfonamide
 2-propyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]furfur-2-yl]-3,4-
 difluorobenzamide
 2-propyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-
 chlorophenylsulfonamide
 2-propyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]furfur-2-yl]-p-
 nitrobenzamide
 2-propyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-
 phenylsulfonamide
 2-propyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]furfur-2-yl]-p-
 nitrobenzamide
 2-propyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-
 bromomethylphenylsulfonamide
 2-propyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]furfur-2-yl]-m-
 nitrobenzamide
 2-propyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-
 phenylsulfonamide
 2-propyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]furfur-2-yl]-m-
 nitrobenzamide
 2-propyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-
 phenylsulfonamide
 2-propyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]furfur-2-yl]-m-
 nitrobenzamide
 2-propyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-
 phenylsulfonamide

- N-[5-[(α -Cyclopropyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]furfur-2-yl]-m-trifluoromethylphenylsulfonamide
- N-[5-[(α -Cyclopropyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-ylmethyl]-m-trifluoromethylphenylsulfonamide
- 5 N-[5-[(α -Cyclopropyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]furfur-2-yl]-o-fluorophenylsulfonamide
- N-[5-[(α -Cyclopropyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-ylmethyl]-o-fluorophenylsulfonamide
- N-[5-[(α -Cyclopropyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]furfur-2-yl]-o-chlorophenylsulfonamide
- 10 N-[5-[(α -Cyclopropyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-ylmethyl]-o-chlorophenylsulfonamide
- N-[5-[(α -Cyclopropyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]furfur-2-yl]-o-cyanophenylsulfonamide
- 15 N-[5-[(α -Cyclopropyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-ylmethyl]-o-cyanophenylsulfonamide
- N-[5-[(α -Cyclopropyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]furfur-2-yl]-o-trifluoromethylphenylsulfonamide
- N-[5-[(α -Cyclopropyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-ylmethyl]-o-trifluoromethylphenylsulfonamide
- 20 N-[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]furfur-2-yl]-phenylsulfonamide
- N-[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-ylmethyl]-phenylsulfonamide
- 25 N-[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]furfur-2-yl]-p-fluorophenylsulfonamide
- N-[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-ylmethyl]-p-fluorophenylsulfonamide
- N-[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]furfur-2-yl]-p-chlorophenylsulfonamide
- 30 N-[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-ylmethyl]-p-chlorophenylsulfonamide
- N-[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]furfur-2-yl]-3,4-dichlorophenylsulfonamide
- 35 N-[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-ylmethyl]-3,4-dichlorophenylsulfonamide

- N-[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]furfur-2-yl]-p-cyanophenylsulfonamide
- N-[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide
- 5 N-[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]furfur-2-yl]-p-trifluoromethylphenylsulfonamide
- N-[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-ylmethyl]-p-trifluoromethylphenylsulfonamide
- N-[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]furfur-2-yl]-m-
- 10 fluorophenylsulfonamide
- N-[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-ylmethyl]-m-fluorophenylsulfonamide
- N-[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]furfur-2-yl]-m-chlorophenylsulfonamide
- 15 N-[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-ylmethyl]-m-chlorophenylsulfonamide
- N-[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]furfur-2-yl]-m-cyanophenylsulfonamide
- N-[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-ylmethyl]-m-
- 20 cyanophenylsulfonamide
- N-[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]furfur-2-yl]-m-trifluoromethylphenylsulfonamide
- N-[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-ylmethyl]-m-trifluoromethylphenylsulfonamide
- 25 N-[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]furfur-2-yl]-o-fluorophenylsulfonamide
- N-[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-ylmethyl]-o-fluorophenylsulfonamide
- N-[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]furfur-2-yl]-o-
- 30 chlorophenylsulfonamide
- N-[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-ylmethyl]-o-chlorophenylsulfonamide
- N-[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]furfur-2-yl]-o-
- 35 cyanophenylsulfonamide
- N-[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-ylmethyl]-o-cyanophenylsulfonamide

- N-[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl)furfur-2-yl]-o-trifluoromethylphenylsulfonamide
- N-[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-ylmethyl]-o-trifluoromethylphenylsulfonamide
- 5 3-(α [S]-Cyclopropyl(m-fluorobenzyl))-4-hydroxy-6-(α [R]-ethyl- β -tetrahydropyran-4-yl)ethyl-2H-pyran-2-one
- 3-(α [S]-Cyclopropyl(m-fluorobenzyl))-4-hydroxy-6-(α [S]-ethyl- β -tetrahydropyran-4-yl)ethyl-2H-pyran-2-one
- 3-(α [S]-Cyclopropyl(m-fluorobenzyl))-4-hydroxy-6-(α [R]-ethyl- β -tetrahydropyran-4-yl)ethyl-2H-pyran-2-one
- 10 3-(α [S]-Cyclopropyl(m-fluorobenzyl))-4-hydroxy-6-(α [S]-ethyl- β -tetrahydropyran-4-yl)ethyl-2H-pyran-2-one
- 3-(α [R]-Cyclopropyl(m-fluorobenzyl))-4-hydroxy-6-(α [R]-ethyl- β -tetrahydropyran-4-yl)ethyl-2H-pyran-2-one
- 15 3-(α [R]-Cyclopropyl(m-fluorobenzyl))-4-hydroxy-6-(α [S]-ethyl- β -tetrahydropyran-4-yl)ethyl-2H-pyran-2-one
- 3-(α [R]-Cyclopropyl(m-fluorobenzyl))-4-hydroxy-6-(α [R]-ethyl- β -tetrahydropyran-4-yl)ethyl-2H-pyran-2-one
- 3-(α [R]-Cyclopropyl(m-fluorobenzyl))-4-hydroxy-6-(α [S]-ethyl- β -tetrahydropyran-4-yl)ethyl-2H-pyran-2-one
- 20 N-[5-[α [R]-Ethyl- α -(6-(α [R]-ethyl- α [S]-tetrahydrofuran-2-ylmethyl)methyl-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide
- N-[5-[α [R]-Ethyl- α -(6-(α [R]-ethyl- α [R]-tetrahydrofuran-2-ylmethyl)methyl-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide
- 25 N-[5-[α [R]-Ethyl- α -(6-(α [R]-ethyl- α [S]-tetrahydrofuran-2-ylmethyl)methyl-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-ylmethyl]-p-fluorophenylsulfonamide
- N-[5-[α [R]-Ethyl- α -(6-(α [R]-ethyl- α [R]-tetrahydrofuran-2-ylmethyl)methyl-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-ylmethyl]-p-fluorophenylsulfonamide
- N-[5-[α [R]-Ethyl- α -(6-(1[S]-ethyl-2[R]-hydroxy-2-[S]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide
- 30 N-[5-[α [R]-Ethyl- α -(6-(1[S]-ethyl-2[R]-hydroxy-2-[R]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide
- N-[5-[α [R]-Ethyl- α -(6-(1[R]-ethyl-2[S]-hydroxy-2-[S]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide
- 35 N-[5-[α [R]-Ethyl- α -(6-(1[R]-ethyl-2[S]-hydroxy-2-[R]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide

- N-[5-[α (R)-Ethyl- α -[6-(1[S]-ethyl-2[S]-hydroxy-2-[S]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide
- N-[5-[α (R)-Ethyl- α -[6-(1[S]-ethyl-2[S]-hydroxy-2-[R]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide
- 5 N-[5-[α (R)-Ethyl- α -[6-(1[R]-ethyl-2[R]-hydroxy-2-[S]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide
- N-[5-[α (R)-Ethyl- α -[6-(1[R]-ethyl-2[R]-hydroxy-2-[R]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide
- N-[5-[α (S)-Ethyl- α -[6-(1[S]-ethyl-2[R]-hydroxy-2-[S]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide
- 10 N-[5-[α (S)-Ethyl- α -[6-(1[S]-ethyl-2[R]-hydroxy-2-[R]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide
- N-[5-[α (S)-Ethyl- α -[6-(1[R]-ethyl-2[S]-hydroxy-2-[S]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide
- 15 N-[5-[α (S)-Ethyl- α -[6-(1[R]-ethyl-2[S]-hydroxy-2-[R]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide
- N-[5-[α (S)-Ethyl- α -[6-(1[S]-ethyl-2[S]-hydroxy-2-[S]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide
- 20 N-[5-[α (S)-Ethyl- α -[6-(1[R]-ethyl-2[R]-hydroxy-2-[S]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide
- N-[5-[α (S)-Ethyl- α -[6-(1[R]-ethyl-2[R]-hydroxy-2-[R]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide
- 25 N-[5-[α (R)-Cyclopropyl- α -[6-(α (R)-ethyl- α (S)-tetrahydrofuran-2-ylmethyl)methyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide
- N-[5-[α (R)-Cyclopropyl- α -[6-(α (R)-ethyl- α (R)-tetrahydrofuran-2-ylmethyl)methyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide
- N-[5-[α (R)-Cyclopropyl- α -[6-(α (R)-ethyl- α (S)-tetrahydrofuran-2-ylmethyl)methyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-fluorophenylsulfonamide
- 30 N-[5-[α (R)-Cyclopropyl- α -[6-(α (R)-ethyl- α (R)-tetrahydrofuran-2-ylmethyl)methyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-fluorophenylsulfonamide
- N-[5-[α (R)-Cyclopropyl- α -[6-(1[S]-ethyl-2[R]-hydroxy-2-[S]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide
- 35 N-[5-[α (R)-Cyclopropyl- α -[6-(1[S]-ethyl-2[R]-hydroxy-2-[R]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide

- N-[5-[α (R)-Cyclopropyl- α -[6-(1(R)-ethyl-2(S)-hydroxy-2-[S]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide
- N-[5-[α (R)-Cyclopropyl- α -[6-(1(R)-ethyl-2(S)-hydroxy-2-[R]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide
- 5 N-[5-[α (R)-Cyclopropyl- α -[6-(1(S)-ethyl-2(S)-hydroxy-2-[S]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide
- N-[5-[α (R)-Cyclopropyl- α -[6-(1(S)-ethyl-2(S)-hydroxy-2-[R]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide
- N-[5-[α (R)-Cyclopropyl- α -[6-(1(R)-ethyl-2(R)-hydroxy-2-[S]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide
- 10 N-[5-[α (R)-Cyclopropyl- α -[6-(1(R)-ethyl-2(R)-hydroxy-2-[R]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide
- N-[5-[α (S)-Cyclopropyl- α -[6-(1(S)-ethyl-2(R)-hydroxy-2-[S]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide
- 15 N-[5-[α (S)-Cyclopropyl- α -[6-(1(S)-ethyl-2(R)-hydroxy-2-[R]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide
- N-[5-[α (S)-Cyclopropyl- α -[6-(1(R)-ethyl-2(S)-hydroxy-2-[S]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide
- N-[5-[α (S)-Cyclopropyl- α -[6-(1(R)-ethyl-2(S)-hydroxy-2-[R]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide
- 20 N-[5-[α (S)-Cyclopropyl- α -[6-(1(S)-ethyl-2(S)-hydroxy-2-[S]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide
- N-[5-[α (S)-Cyclopropyl- α -[6-(1(S)-ethyl-2(S)-hydroxy-2-[R]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide
- 25 N-[5-[α (S)-Cyclopropyl- α -[6-(1(R)-ethyl-2(R)-hydroxy-2-[S]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide
- N-[5-[α (S)-Cyclopropyl- α -[6-(1(R)-ethyl-2(R)-hydroxy-2-[R]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide
- 30 3-(α (S)-Cyclopropyl(5-(2-hydroxyethyl))thiophen-2-ylmethyl)-6-(1(R)-ethyl-2-[R]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2H-pyran-2-one
- 3-(α (S)-Cyclopropyl(5-(2-hydroxyethyl))thiophen-2-ylmethyl)-6-(α (R)-ethylphenethyl)-4-hydroxy-2H-pyran-2-one
- 3-(α (S)-Cyclopropyl(5-(2-hydroxyethyl))thiophen-2-ylmethyl)-6-(α (R)-ethyl-meta-hydroxymethylphenethyl)-4-hydroxy-2H-pyran-2-one
- 35 3-(α (S)-Cyclopropyl(5-(2-hydroxyethyl))thiophen-2-ylmethyl)-6-(α (R)-ethyl-ortho-hydroxymethylphenethyl)-4-hydroxy-2H-pyran-2-one

- 3-(α [S]-Cyclopropyl(5-(1,2-dihydroxyethyl))thiophen-2-ylmethyl)-6-(1[R]-ethyl-2-[R]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2H-pyran-2-one
- 3-(α [S]-Cyclopropyl(5-(1,2-dihydroxyethyl))thiophen-2-ylmethyl)-6-(α [R]-ethylphenethyl)-4-hydroxy-2H-pyran-2-one
- 5 3-(α [S]-Cyclopropyl(5-(1,2-dihydroxyethyl))thiophen-2-ylmethyl)-6-(α [R]-ethyl-meta-hydroxymethylphenethyl)-4-hydroxy-2H-pyran-2-one
- 3-(α [S]-Cyclopropyl(5-(1,2-dihydroxyethyl))thiophen-2-ylmethyl)-6-(α [R]-ethyl-ortho-hydroxymethylphenethyl)-4-hydroxy-2H-pyran-2-one
- 3-(α [S]-Cyclopropyl)-meta-(4-cyanophenylsulfonylamino)benzyl)-6-(α [R]-ethylphenethyl)-4-hydroxy-2H-pyran-2-one (Refer to Chart BBB)
- 10 3-(α [S]-Cyclopropyl)-meta-(4-cyanophenylsulfonylamino)benzyl)-6-(α [S]-ethylphenethyl)-4-hydroxy-2H-pyran-2-one (Formula BBB-13) Refer to Chart BBB
- 3-(α [R]-Cyclopropyl)-meta-(4-cyanophenylsulfonylamino)benzyl)-6-(α [S]-ethylphenethyl)-4-hydroxy-2H-pyran-2-one (Formula BBB-11) Refer to Chart BBB
- 15 3-(α [R]-Cyclopropyl)-meta-(4-cyanophenylsulfonylamino)benzyl)-6-(α [R]-ethylphenethyl)-4-hydroxy-2H-pyran-2-one (Refer to Chart BBB)
- 3-([(R)-Cyclopropylmethyl)(5-N-(p-fluorophenylsulfonyl)methyl)thiophenemercapto-2-yl]-6-(α [R]-ethylphenethyl)-4-hydroxy-2H-pyran-2-one (Formula DDD-6) Refer to Chart DDD
- 3-(α -Cyclopropyl-meta-(4-fluorophenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one
- 20 3-(α -Cyclopropyl-meta-(benzothiadiazolyl-sulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one
- 3-(α -Cyclopropyl-meta-(benzo-oxadiazolyl-sulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one
- 25 3-(α -Cyclopropyl-meta-((1-methyl-imidazol-4-yl)-sulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one
- 3-(α -Cyclopropyl-meta-(pyridine-3-yl)-sulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one
- 3-(α -Cyclopropyl-meta-(5-(pyridine-2-yl)-thiophene-2-yl-sulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one
- 30 3-(α -Cyclopropyl-meta-(4-hydroxyaminophenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one
- 3-(α -Cyclopropyl-meta-(4-dimethylaminophenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one
- 35 3-(α -Cyclopropyl-meta-(3-aminophenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-

2H-pyran-2-one

3-(α -Cyclopropyl-*meta*-(4-aminocarbonylphenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one

3-(α -Cyclopropylbenzyl)-6-(α -ethyl-phenylsulfonylaminoethyl)-4-hydroxy-2H-pyran-2-one

5 3-(α -Cyclopropylbenzyl)-6-(1-ethyl-2-phenylsulfonylamino-ethyl)-4-hydroxy-2H-pyran-2-one

3-(α -Cyclopropyl-*meta*-(4-fluorophenylsulfonylamino)benzyl)-6-(α -ethyl-phenylsulfonylaminoethyl)-4-hydroxy-2H-pyran-2-one

3-(α -Cyclopropyl-*meta*-(phenylsulfonylamino)benzyl)-6-(α -ethyl-phenylsulfonylaminoethyl)-4-hydroxy-2H-pyran-2-one

10 3-(α -Cyclopropyl-*meta*-(2,5-dichlorophenylsulfonylamino)benzyl)-6-(α -ethyl-phenylsulfonylaminoethyl)-4-hydroxy-2H-pyran-2-one

3-(α -Cyclopropyl-*meta*-(4-cyanophenylsulfonylamino)benzyl)-6-(α -ethyl-phenylsulfonylaminoethyl)-4-hydroxy-2H-pyran-2-one

3-(α -Cyclopropyl-*meta*-(quinolin-8-yl-sulfonylamino)benzyl)-6-(α -ethyl-phenylsulfonylaminoethyl)-4-hydroxy-2H-pyran-2-one

15 3-(α -Cyclopropyl-*meta*-(2-phenylethenyl)-sulfonylamino)benzyl)-6-(α -ethyl-phenylsulfonylaminoethyl)-4-hydroxy-2H-pyran-2-one

3-(α -Cyclopropyl-*meta*-(1-methyl-imidazo-4-yl)-sulfonylamino)benzyl)-6-(α -ethyl-phenylsulfonylaminoethyl)-4-hydroxy-2H-pyran-2-one

20 3-(α -Cyclopropyl-*meta*-(pyridin-3-yl-sulfonylamino)benzyl)-6-(α -ethyl-phenylsulfonylaminoethyl)-4-hydroxy-2H-pyran-2-one

3-(α -Cyclopropyl-*meta*-(4-dimethylamino-phenylsulfonylamino)benzyl)-6-(α -ethyl-phenylsulfonylaminoethyl)-4-hydroxy-2H-pyran-2-one

3-(α -Cyclopropyl-*meta*-(4-fluorophenylsulfonylamino)benzyl)-6-(1-ethyl-2-phenylsulfonylamino-ethyl)-4-hydroxy-2H-pyran-2-one

25 3-(α -Cyclopropyl-*meta*-(phenylsulfonylamino)benzyl)-6-(1-ethyl-2-phenylsulfonylamino-ethyl)-4-hydroxy-2H-pyran-2-one

3-(α -Cyclopropyl-*meta*-(2,5-dichlorophenylsulfonylamino)benzyl)-6-(1-ethyl-2-phenylsulfonylamino-ethyl)-4-hydroxy-2H-pyran-2-one

30 3-(α -Cyclopropyl-*meta*-(4-cyanophenylsulfonylamino)benzyl)-6-(1-ethyl-2-phenylsulfonylamino-ethyl)-4-hydroxy-2H-pyran-2-one

3-(α -Cyclopropyl-*meta*-(quinolin-8-yl-sulfonylamino)benzyl)-6-(1-ethyl-2-phenylsulfonylamino-ethyl)-4-hydroxy-2H-pyran-2-one

3-(α -Cyclopropyl-*meta*-(2-phenylethenyl)-sulfonylamino)benzyl)-6-(1-ethyl-2-phenylsulfonylamino-ethyl)-4-hydroxy-2H-pyran-2-one

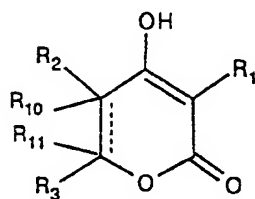
35

- 3-(α -Cyclopropyl-*meta*-((1-methyl-imidazo-4-yl)-sulfonylamino)benzyl)-6-(1-ethyl-2-phenylsulfonylamino-ethyl)-4-hydroxy-2H-pyran-2-one
- 3-(α -Cyclopropyl-*meta*-(pyridin-3-yl-sulfonylamino)benzyl)-6-(1-ethyl-2-phenylsulfonylamino-ethyl)-4-hydroxy-2H-pyran-2-one
- 5 3-(α -Cyclopropyl-*meta*-(4-dimethylamino-phenylsulfonylamino)benzyl)-6-(1-ethyl-2-phenylsulfonylamino-ethyl)-4-hydroxy-2H-pyran-2-one
- (3S,6R) 3-(α -ethyl-4-hydroxybenzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one
- (3S,6R) 3-(α -ethylbenzyl)-6-(α -ethyl-4-hydroxyphenethyl)-4-hydroxy-2H-pyran-2-one
- (3S,6R) 3-(α -ethyl-4-hydroxybenzyl)-6-(α -ethyl-4-hydroxyphenethyl)-4-hydroxy-2H-pyran-2-one
- 10 (3S,6 α R,6 β R) 3-(α -ethylbenzyl)-6-(α -ethyl- β -hydroxyphenethyl)-4-hydroxy-2H-pyran-2-one
- (3S,6 α R,6 β S) 3-(α -ethylbenzyl)-6-(α -ethyl- β -hydroxyphenethyl)-4-hydroxy-2H-pyran-2-one
- (3S,6 α R,6 β R) 3-(α -ethyl-4-hydroxybenzyl)-6-(α -ethyl- β -hydroxyphenethyl)-4-hydroxy-2H-pyran-2-one
- (3S,6 α R,6 β S) 3-(α -ethyl-4-hydroxybenzyl)-6-(α -ethyl- β -hydroxyphenethyl)-4-hydroxy-2H-pyran-2-one
- 15 (3S,6 α R,6 β R) 3-(α -ethylbenzyl)-6-(α -ethyl- β -hydroxy-4-hydroxyphenethyl)-4-hydroxy-2H-pyran-2-one
- (3S,6 α R,6 β S) 3-(α -ethylbenzyl)-6-(α -ethyl- β -hydroxy-4-hydroxyphenethyl)-4-hydroxy-2H-pyran-2-one
- (3S,6 α R,6 β R) 3-(α -ethyl-4-hydroxybenzyl)-6-(α -ethyl- β -hydroxy-4-hydroxyphenethyl)-4-hydroxy-2H-pyran-2-one
- (3S,6 α R,6 β S) 3-(α -ethyl-4-hydroxybenzyl)-6-(α -ethyl- β -hydroxy-4-hydroxyphenethyl)-4-hydroxy-2H-pyran-2-one
- (3S,6R) 3-(α -(1[R]-hydroxyethyl)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one
- 25 (3S,6R) 3-(α -(1[R]-hydroxyethyl)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one
- (3S,6S) 3-(α -ethylbenzyl)-6-(α -(1[R]-hydroxyethyl)phenethyl)-4-hydroxy-2H-pyran-2-one
- (3S,6S) 3-(α -ethylbenzyl)-6-(α -(1[S]-hydroxyethyl)phenethyl)-4-hydroxy-2H-pyran-2-one
- (3S,6S) 3-(α -(1[R]-hydroxyethyl)benzyl)-6-(α -(1[R]-hydroxyethyl)phenethyl)-4-hydroxy-2H-pyran-2-one
- 30 (3S,6S) 3-(α -(1[S]ethyl)benzyl)-6-(α -(1[S]-hydroxyethyl)phenethyl)-4-hydroxy-2H-pyran-2-one
- (3S,6S) 3-(α -(1[R]-hydroxyethyl)benzyl)-6-(α -(1[S]-hydroxyethyl)phenethyl)-4-hydroxy-2H-pyran-2-one
- (3S,6S) 3-(α -(1[S]ethyl)benzyl)-6-(α -(1[R]-hydroxyethyl)phenethyl)-4-hydroxy-2H-pyran-2-one
- (3S,6R) 3-(α -(2-hydroxyethyl)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one
- 35 (3S,6R) 3-(α -ethylbenzyl)-6-(α -(2-hydroxyethyl)phenethyl)-4-hydroxy-2H-pyran-2-one
- (3S,6R) 3-(α -(2-hydroxyethyl)benzyl)-6-(α -(2-hydroxyethyl)phenethyl)-4-hydroxy-2H-pyran-2-one

- 3-(α -ethyl-4-hydroxybenzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one
3-(α -ethylbenzyl)-6-(α -ethyl-4-hydroxyphenethyl)-4-hydroxy-2H-pyran-2-one
3-(α -ethyl-4-hydroxybenzyl)-6-(α -ethyl-4-hydroxyphenethyl)-4-hydroxy-2H-pyran-2-one
3-(α -ethyl-4-hydroxybenzyl)-6-(α -ethyl- β -hydroxyphenethyl)-4-hydroxy-2H-pyran-2-one
5 3-(α -ethylbenzyl)-6-(α -ethyl- β -hydroxy-4-hydroxyphenethyl)-4-hydroxy-2H-pyran-2-one
3-(α -ethyl-4-hydroxybenzyl)-6-(α -ethyl- β -hydroxy-4-hydroxyphenethyl)-4-hydroxy-2H-pyran-2-one
one
3-(α -(1-hydroxyethyl)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one
3-(α -ethylbenzyl)-6-(α -(1-hydroxyethyl)phenethyl)-4-hydroxy-2H-pyran-2-one
10 3-(α -(1-hydroxyethyl)benzyl)-6-(α -(1-hydroxyethyl)phenethyl)-4-hydroxy-2H-pyran-2-one
3-(α -(2-hydroxyethyl)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one
3-(α -ethylbenzyl)-6-(α -(2-hydroxyethyl)phenethyl)-4-hydroxy-2H-pyran-2-one
3-(α -(2-hydroxyethyl)benzyl)-6-(α -(2-hydroxyethyl)phenethyl)-4-hydroxy-2H-pyran-2-one

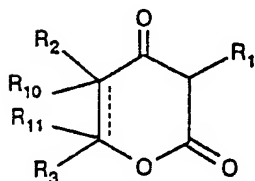
STRUCTURE CHART

5



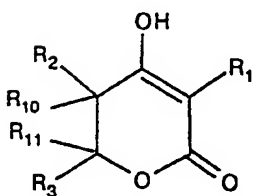
I

10



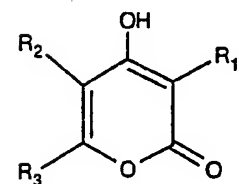
II

15



III

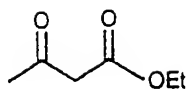
20



IV

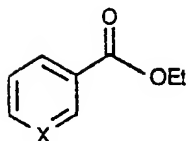
-154-

CHART A

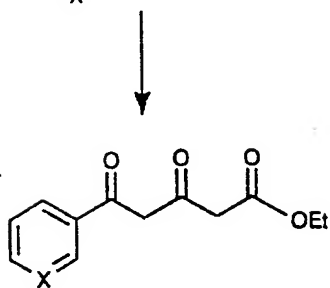


A-1

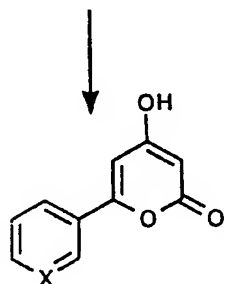
+



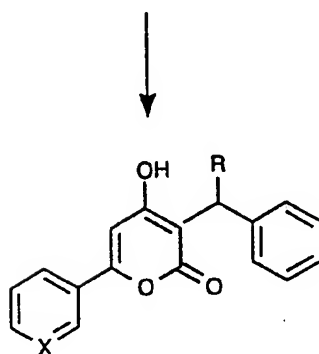
A-2



A-3



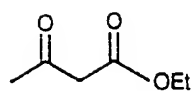
A-4



A-5

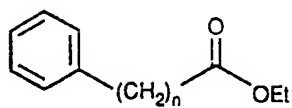
-155-

CHART B

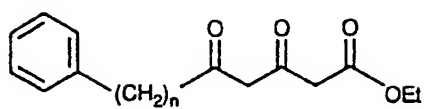


B-1

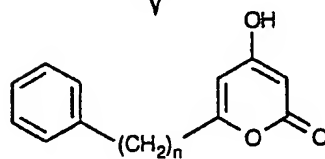
+



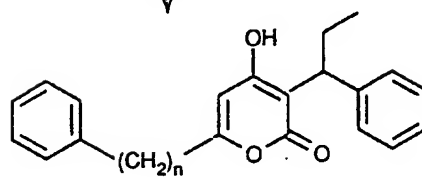
B-2



B-3



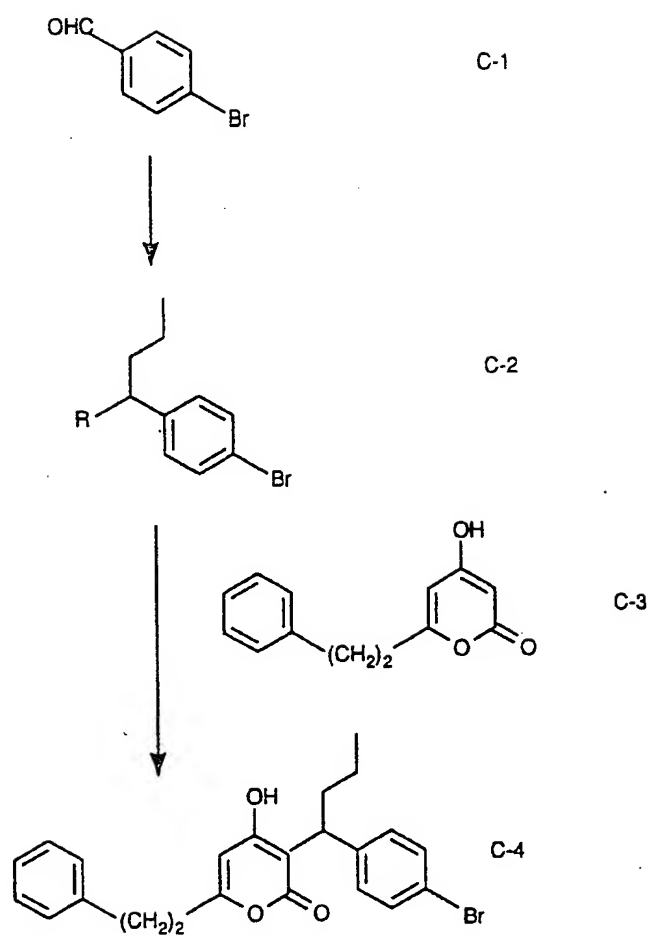
B-4



B-5

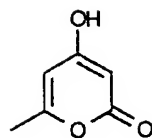
-156-

CHART C

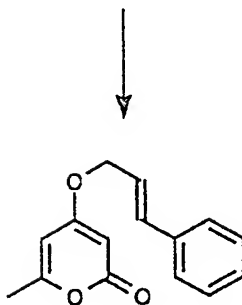


-157-

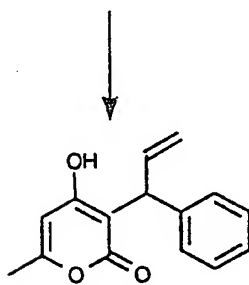
CHART D



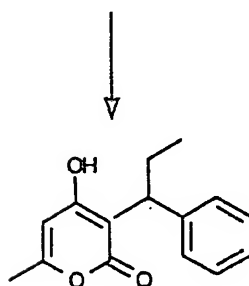
D-1



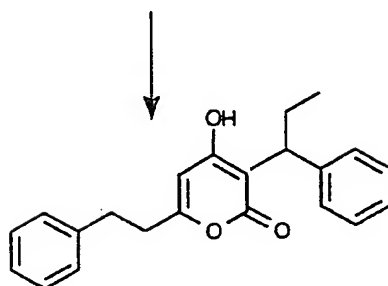
D-2



D-3



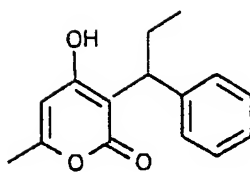
D-4



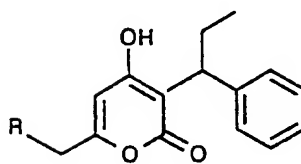
D-5

-158-

CHART E



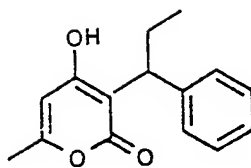
E-1



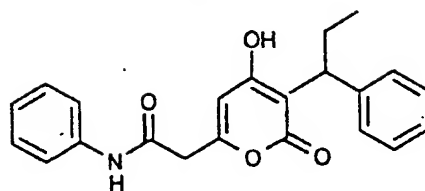
E-2

-159-

CHART F



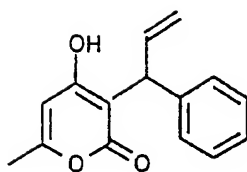
F-1



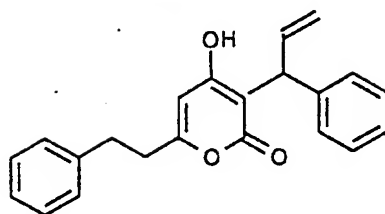
F-2

-160-

CHART G



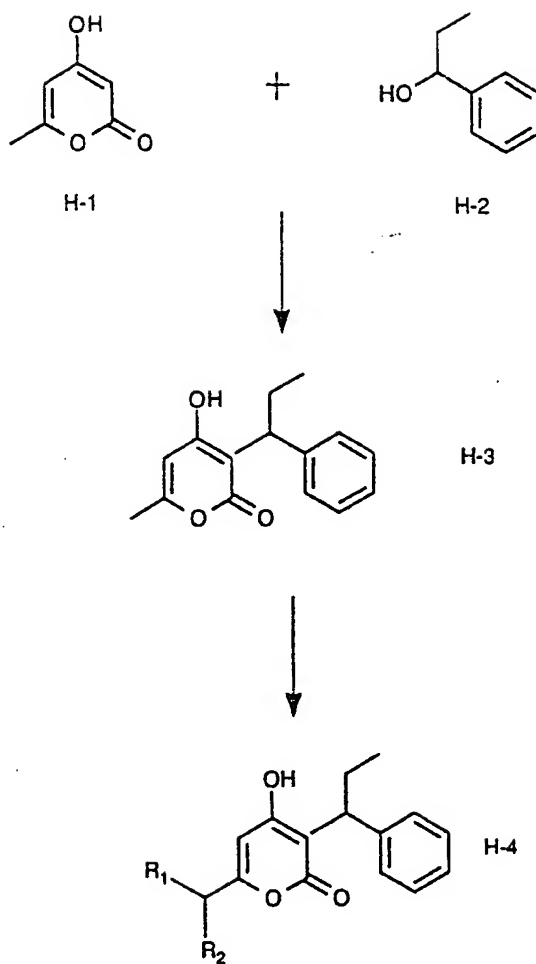
G-1



G-2

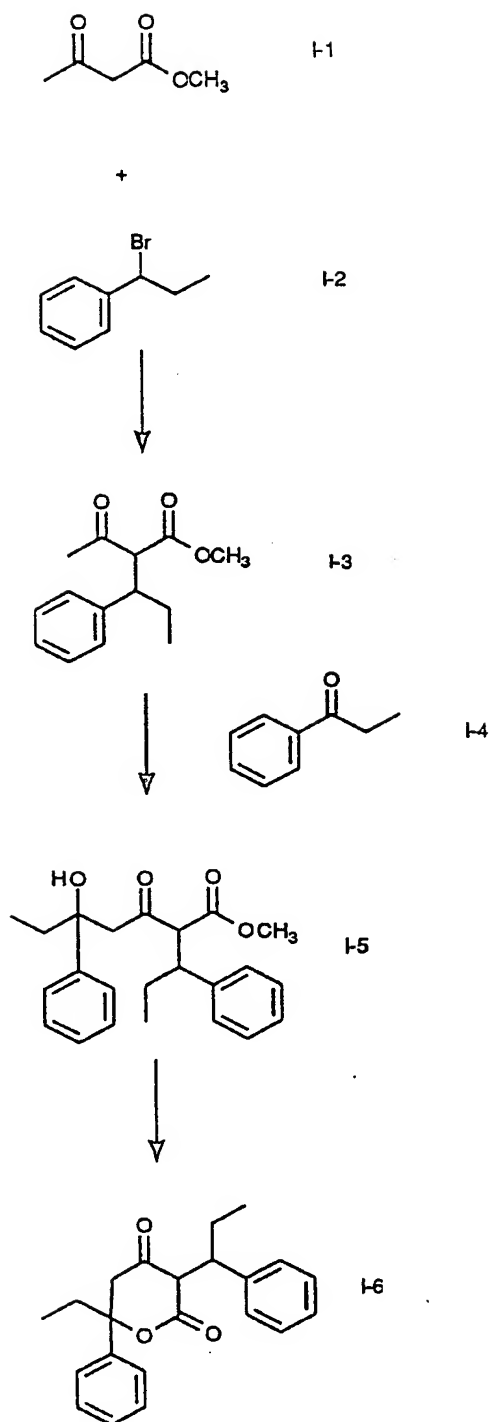
-161-

CHART H



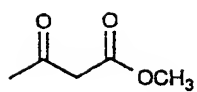
-162-

CHART I



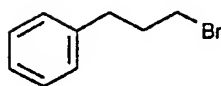
-163-

CHART J

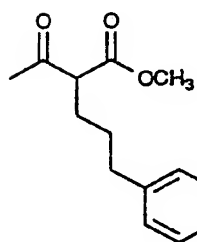


J-1

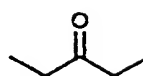
+



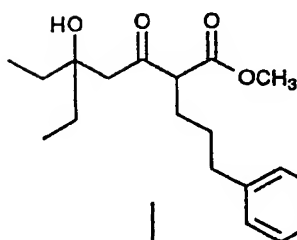
J-2



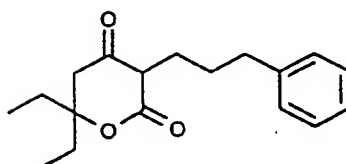
J-3



J-4



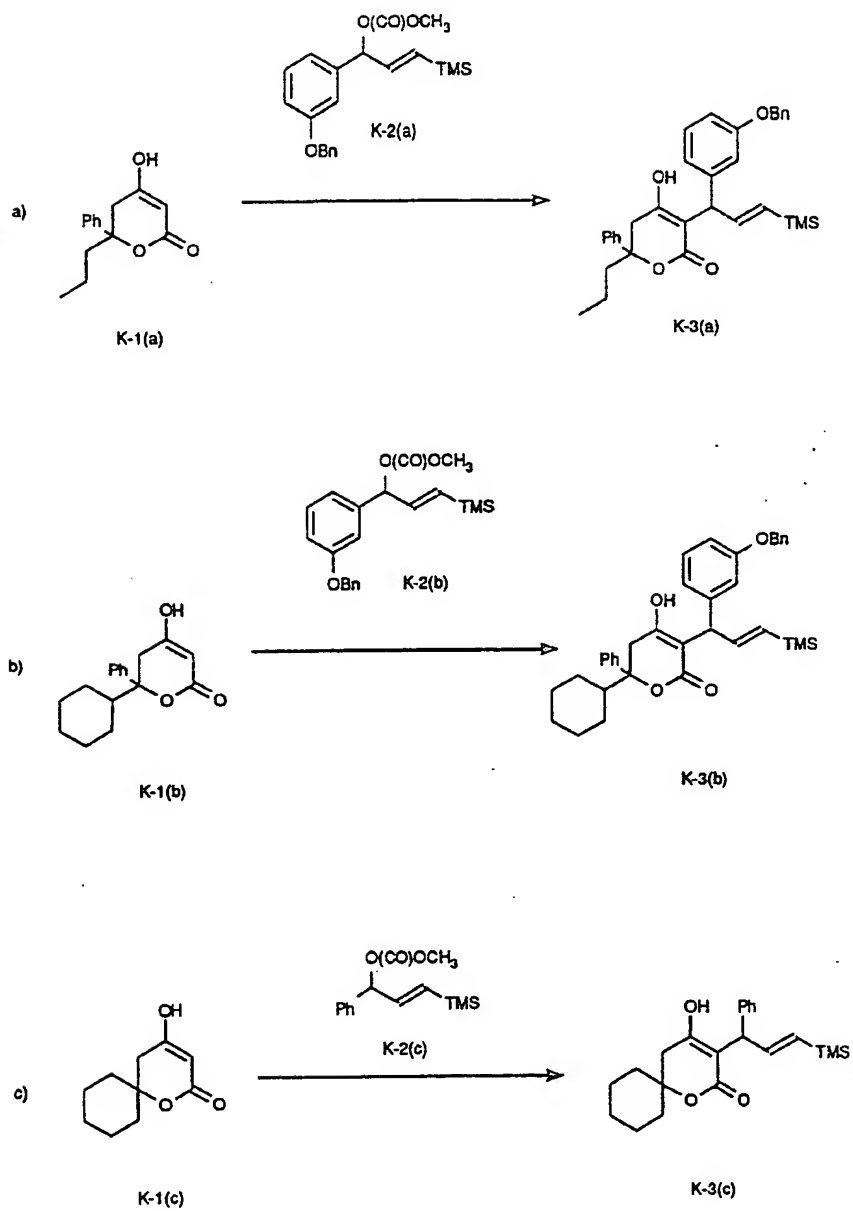
J-5



J-6

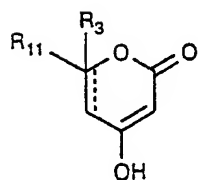
-164-

CHART K



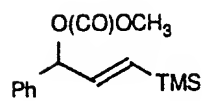
-165-

CHART L

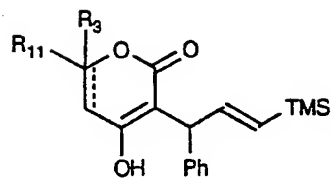


L-1

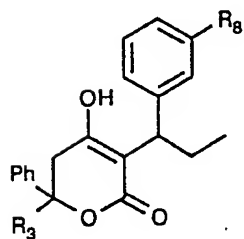
+



L-2



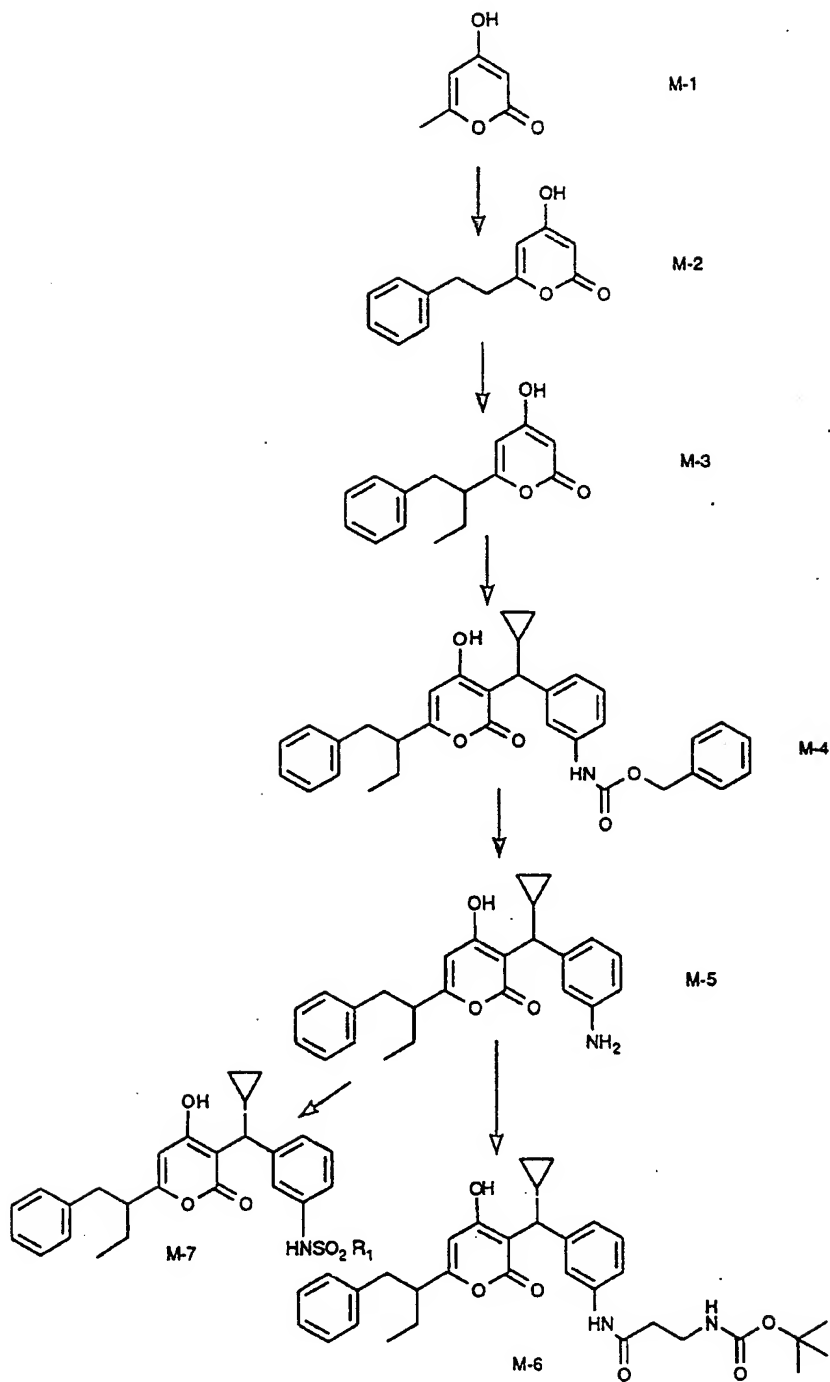
L-3



L-4

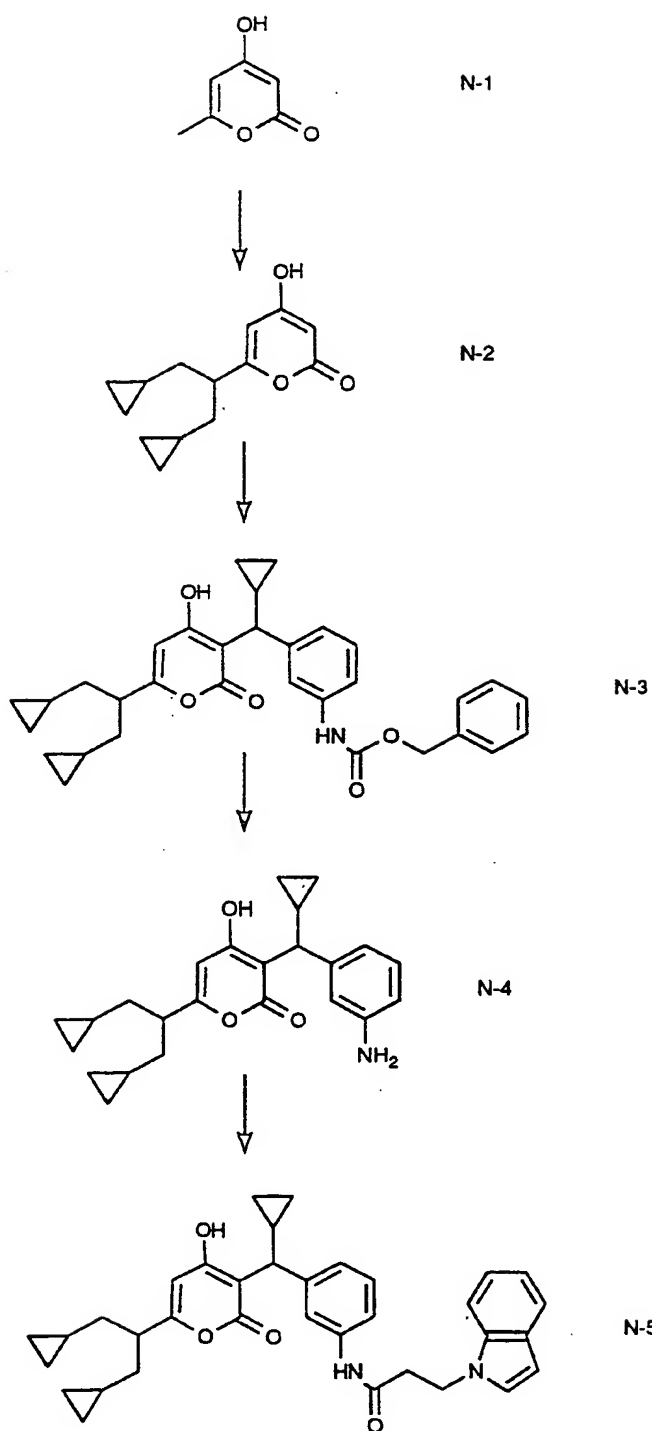
-166-

CHART M



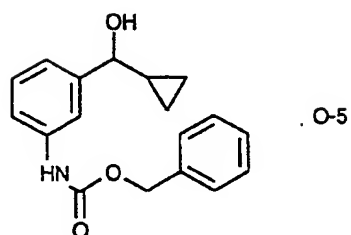
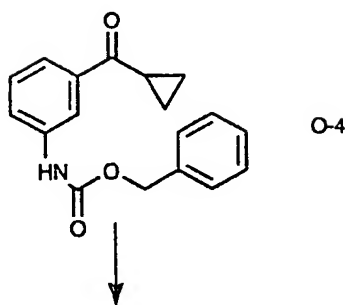
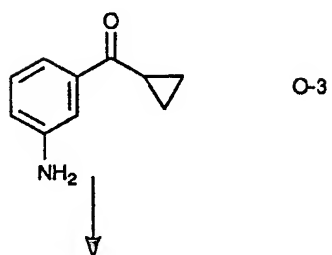
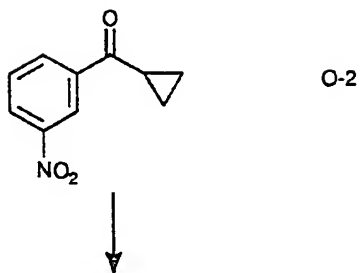
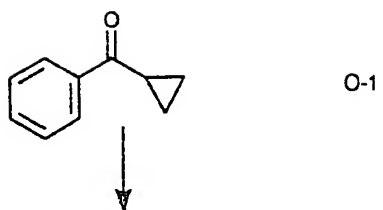
-167-

CHART N



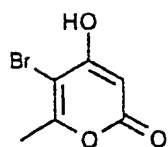
-168-

CHART O

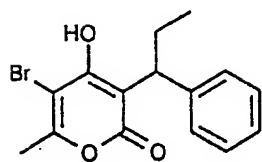


-169-

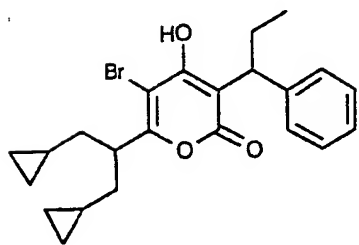
CHART P



P-1



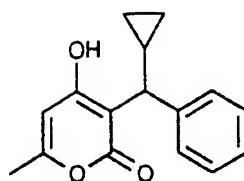
P-2



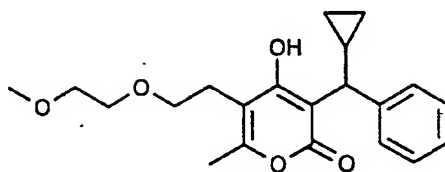
P-3

-170-

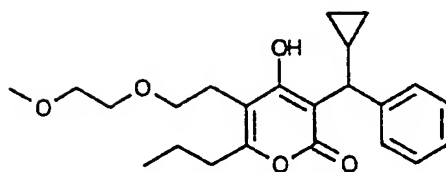
CHART Q



Q-1



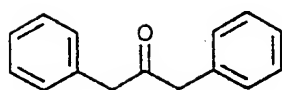
Q-2



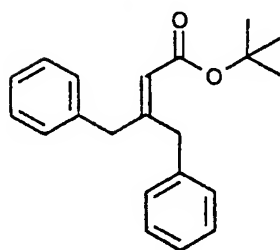
Q-3

-171-

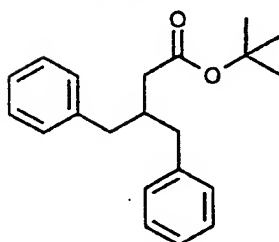
CHART R



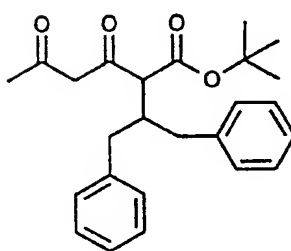
R-1



R-2



R-3

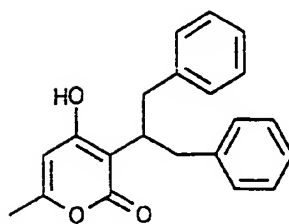


R-4

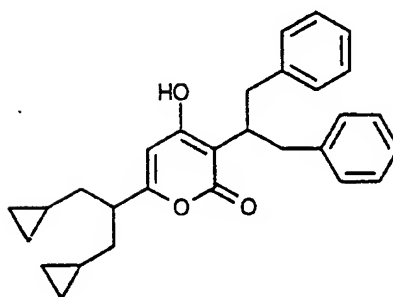


-172-

CHART R (Continued)



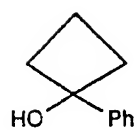
R-5



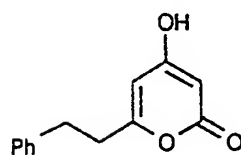
R-6

-173-

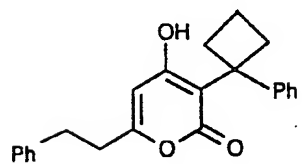
CHART S



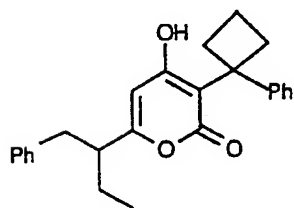
S-1



S-2 (M-2)



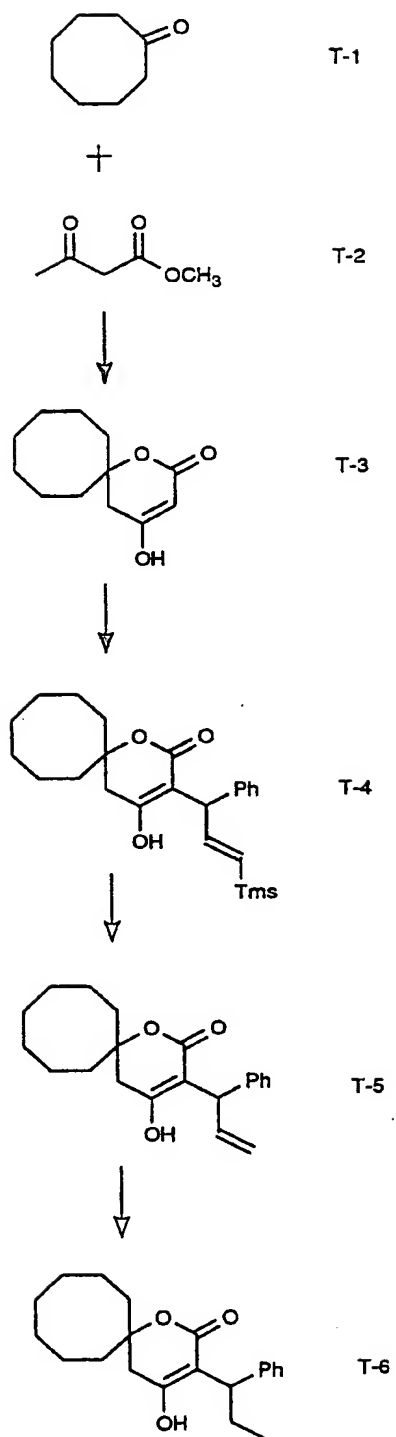
S-3



S-4

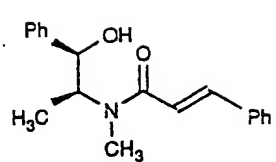
-174-

CHART T

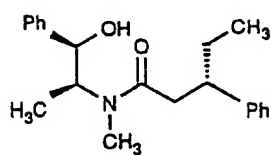


-175-

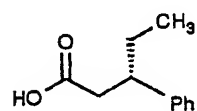
CHART U



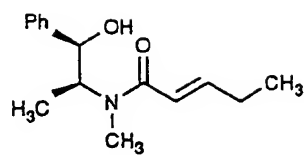
U-1



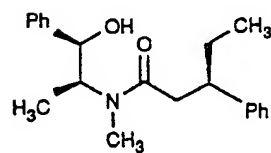
U-2



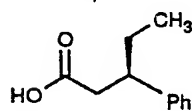
U-3



U-4



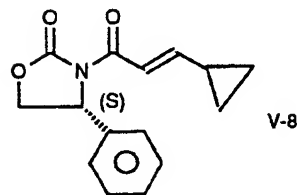
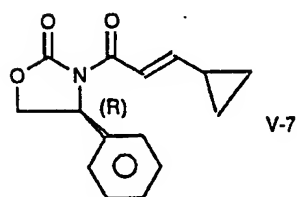
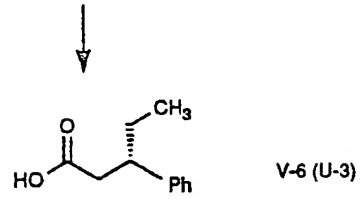
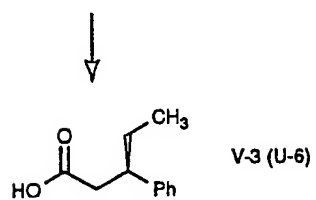
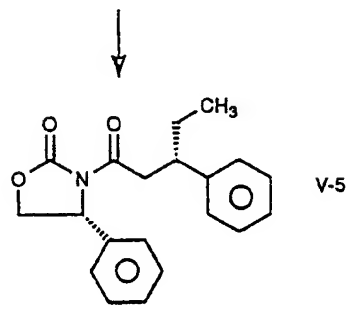
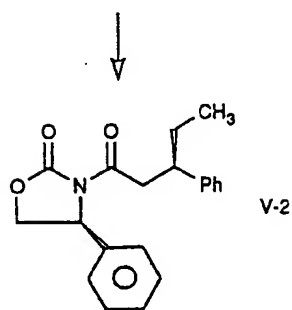
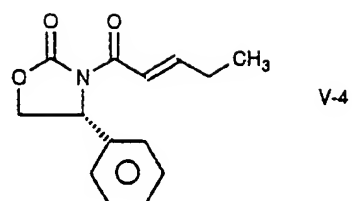
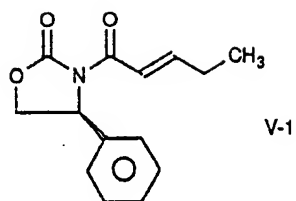
U-5



U-6

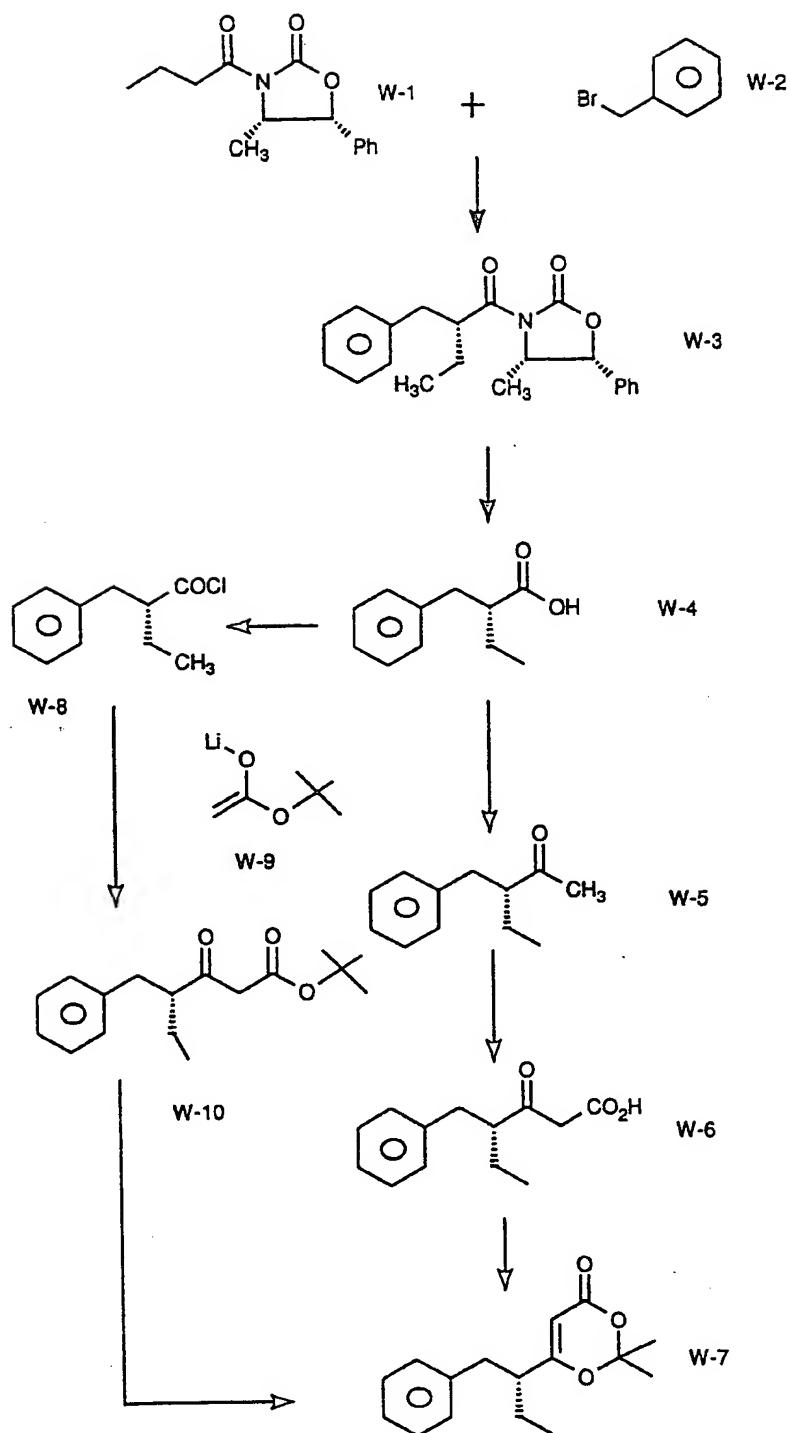
-176-

CHART V



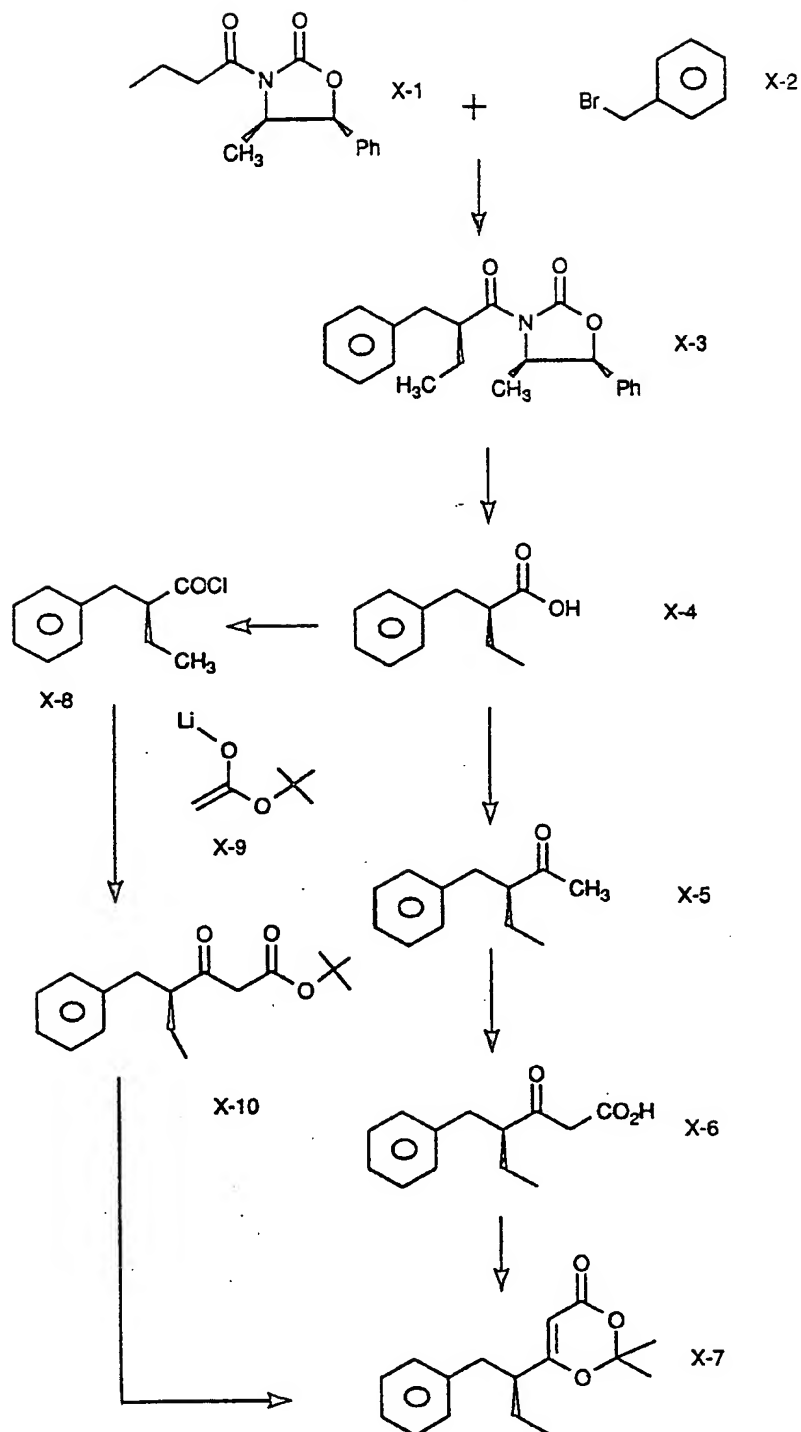
-177-

CHART W



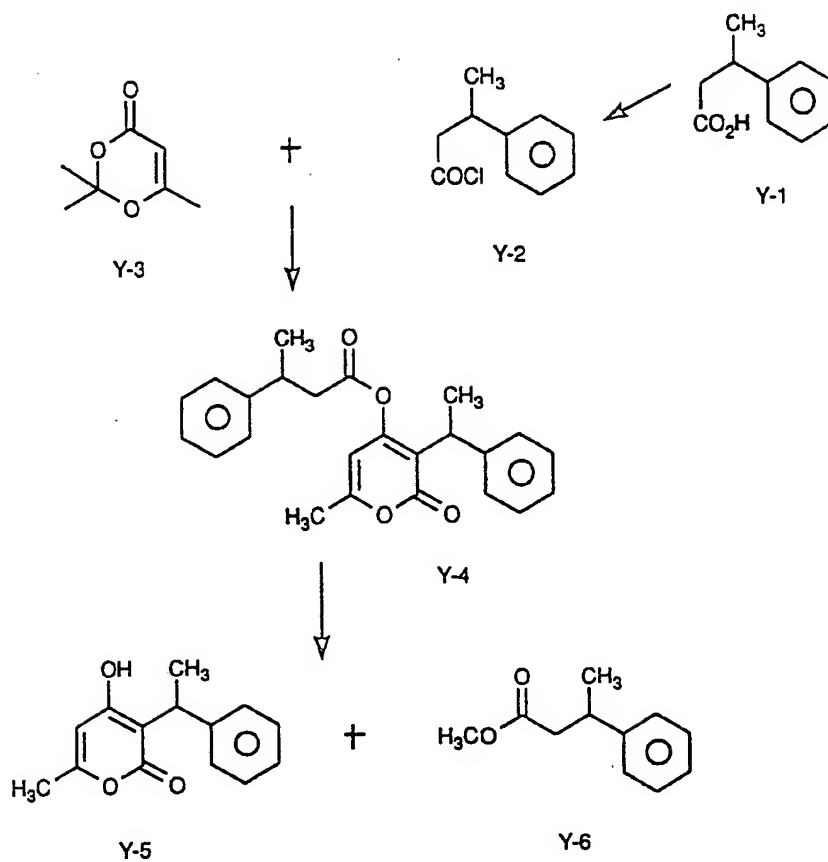
-178-

CHART X



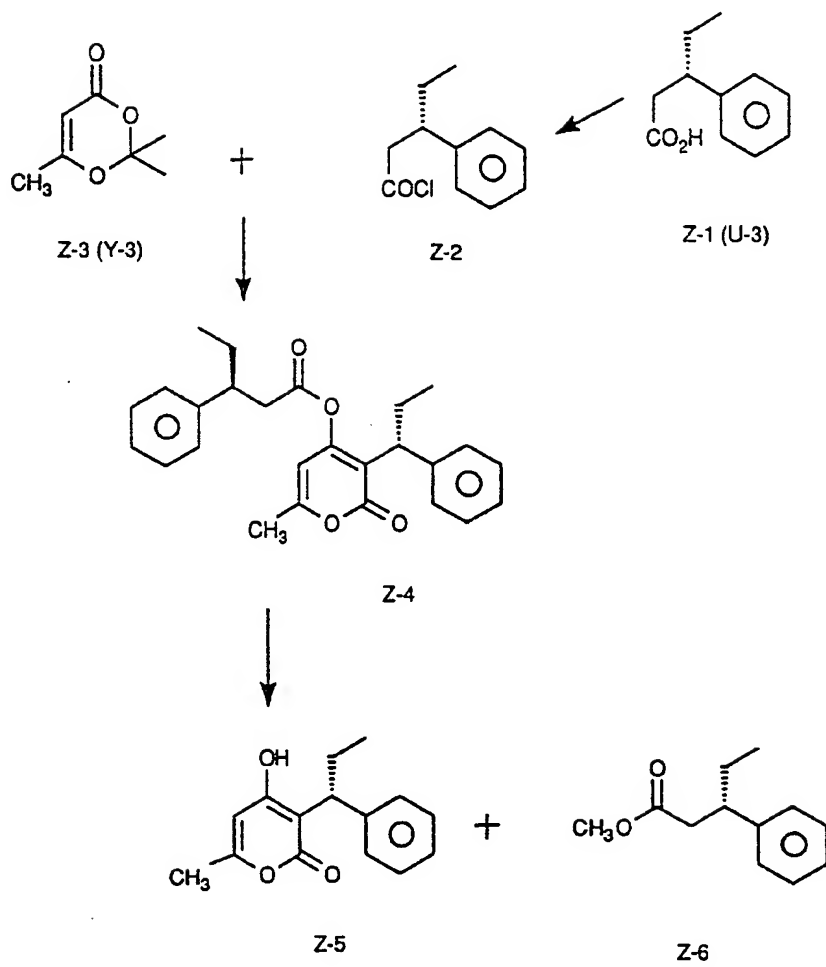
-179-

CHART Y



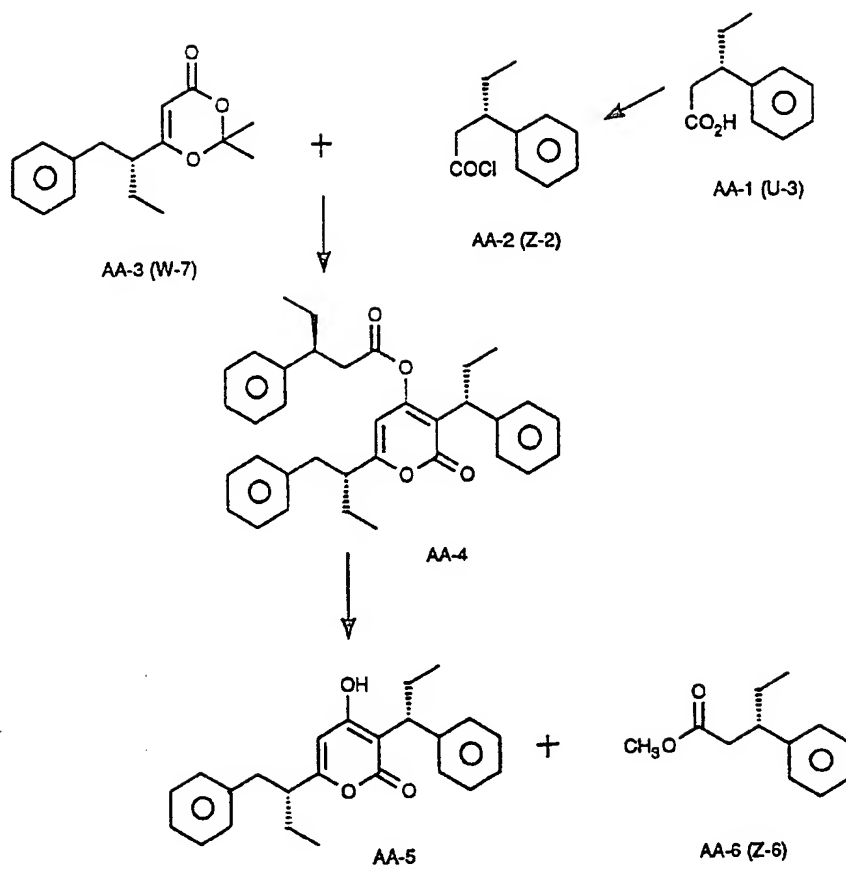
-180-

CHART Z



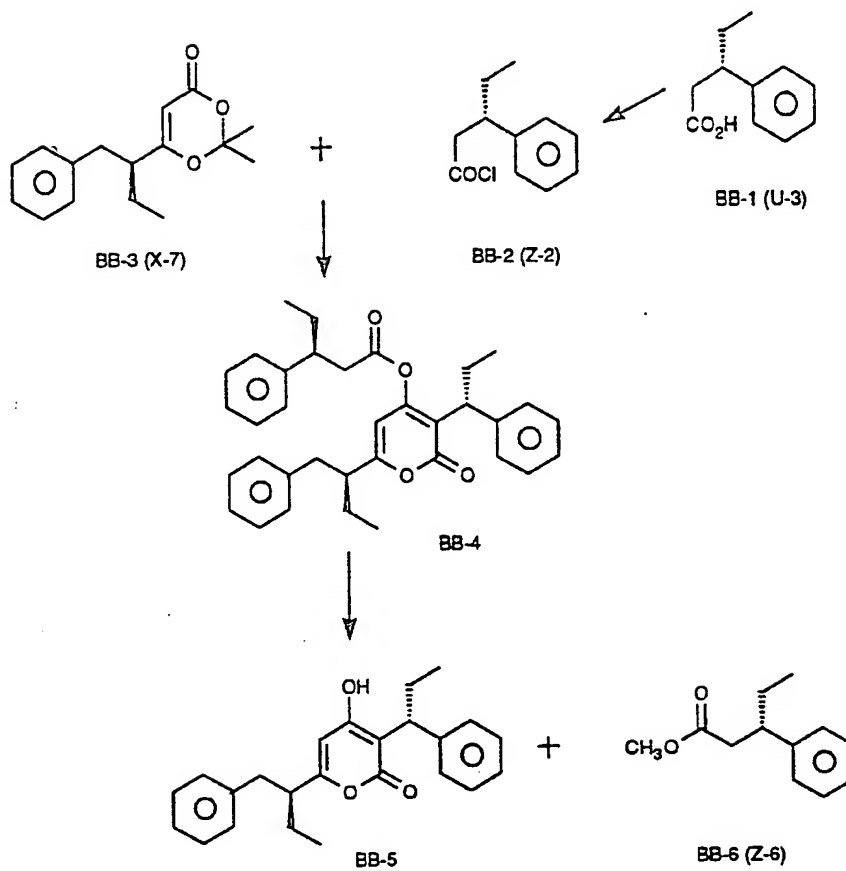
-181-

CHART AA



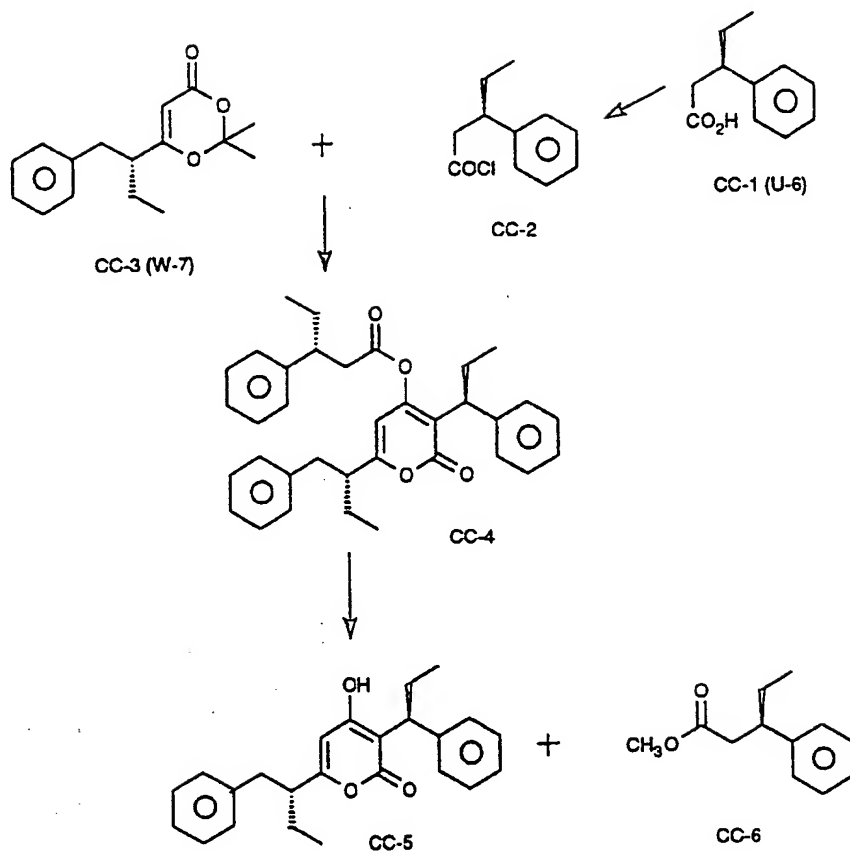
-182-

CHART BB



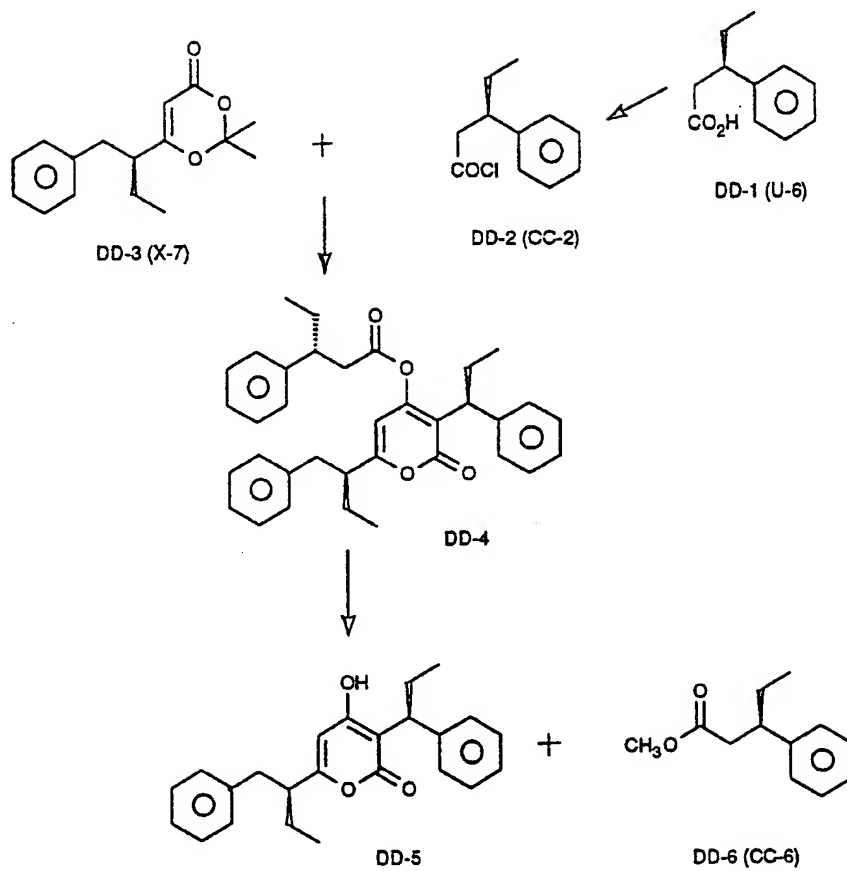
-183-

CHART CC



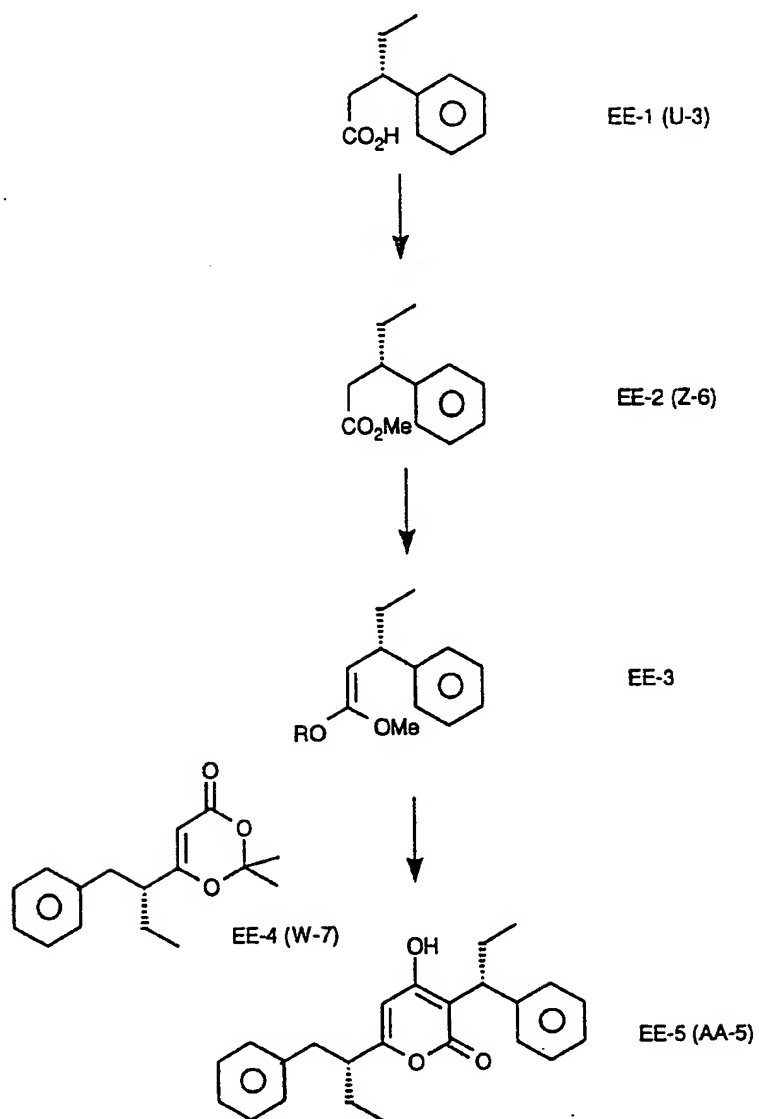
-184-

CHART DD



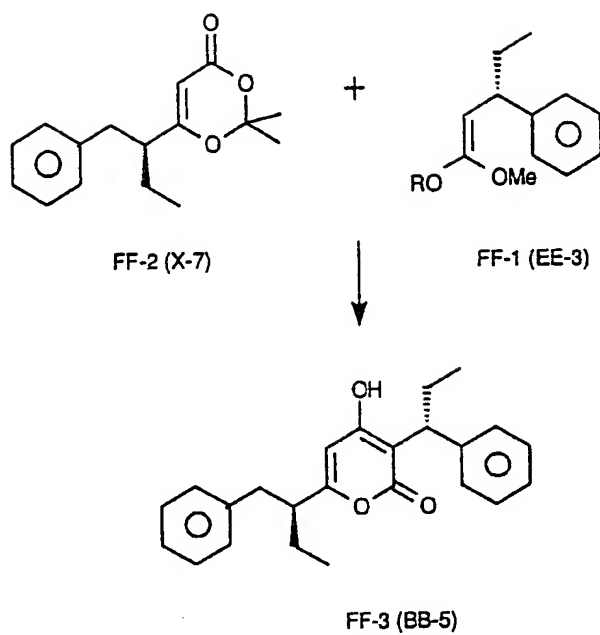
-185-

CHART EE



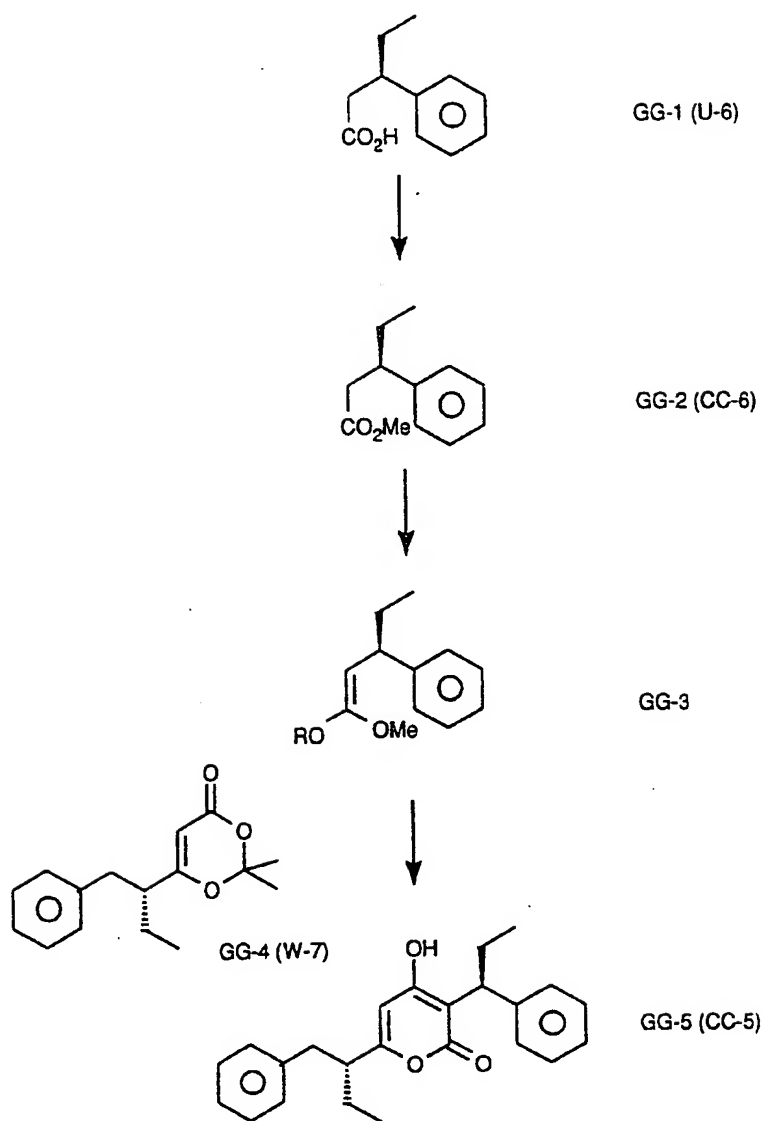
-186-

CHART FF



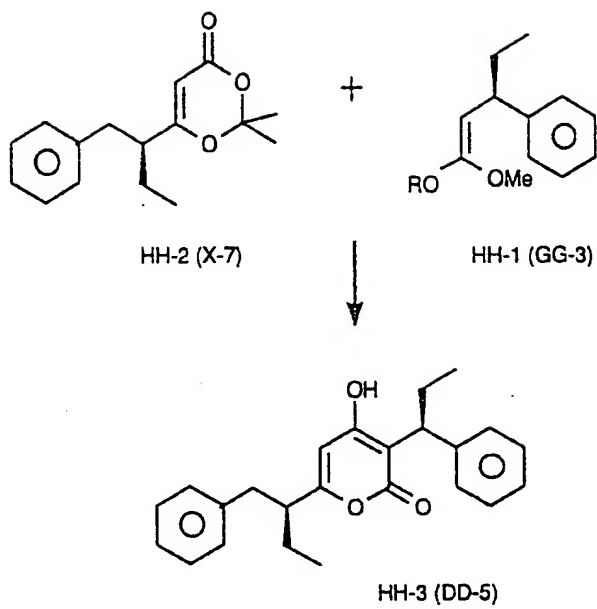
-187-

CHART GG



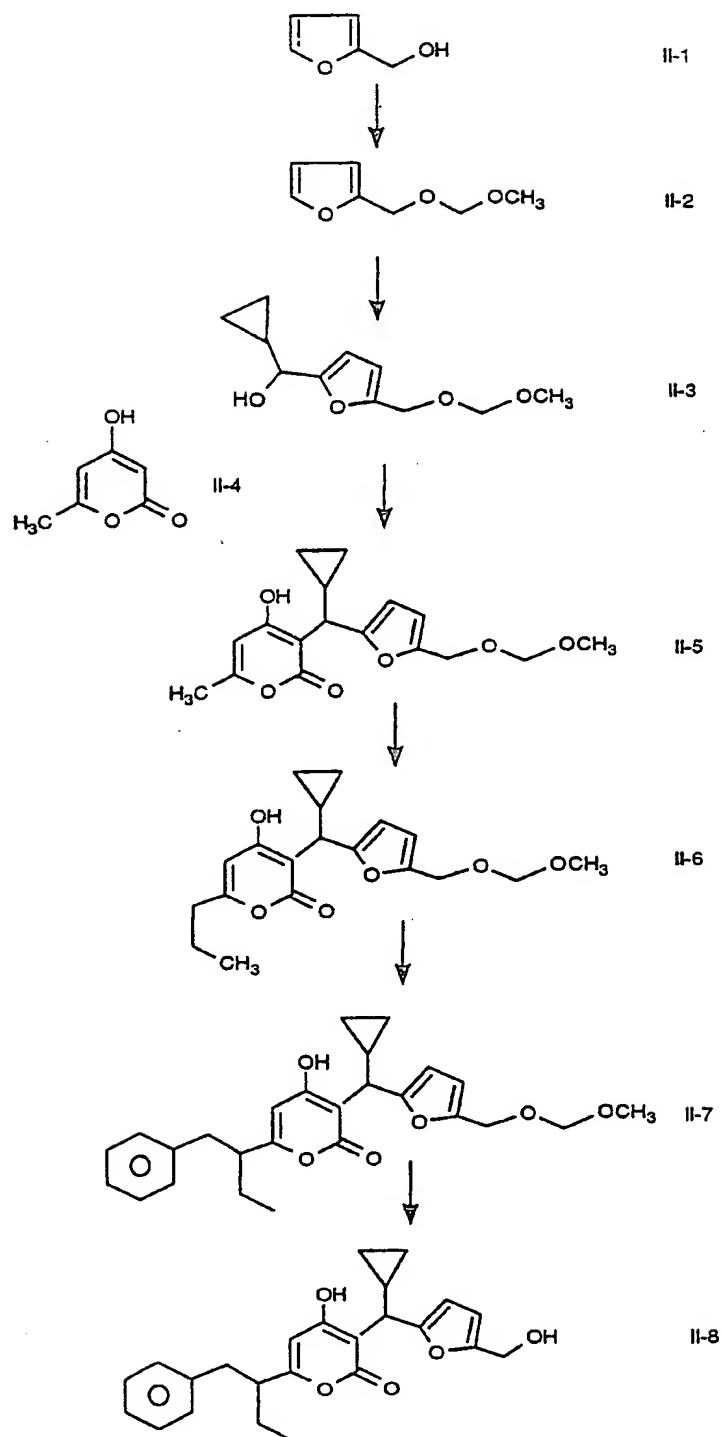
-188-

CHART HH



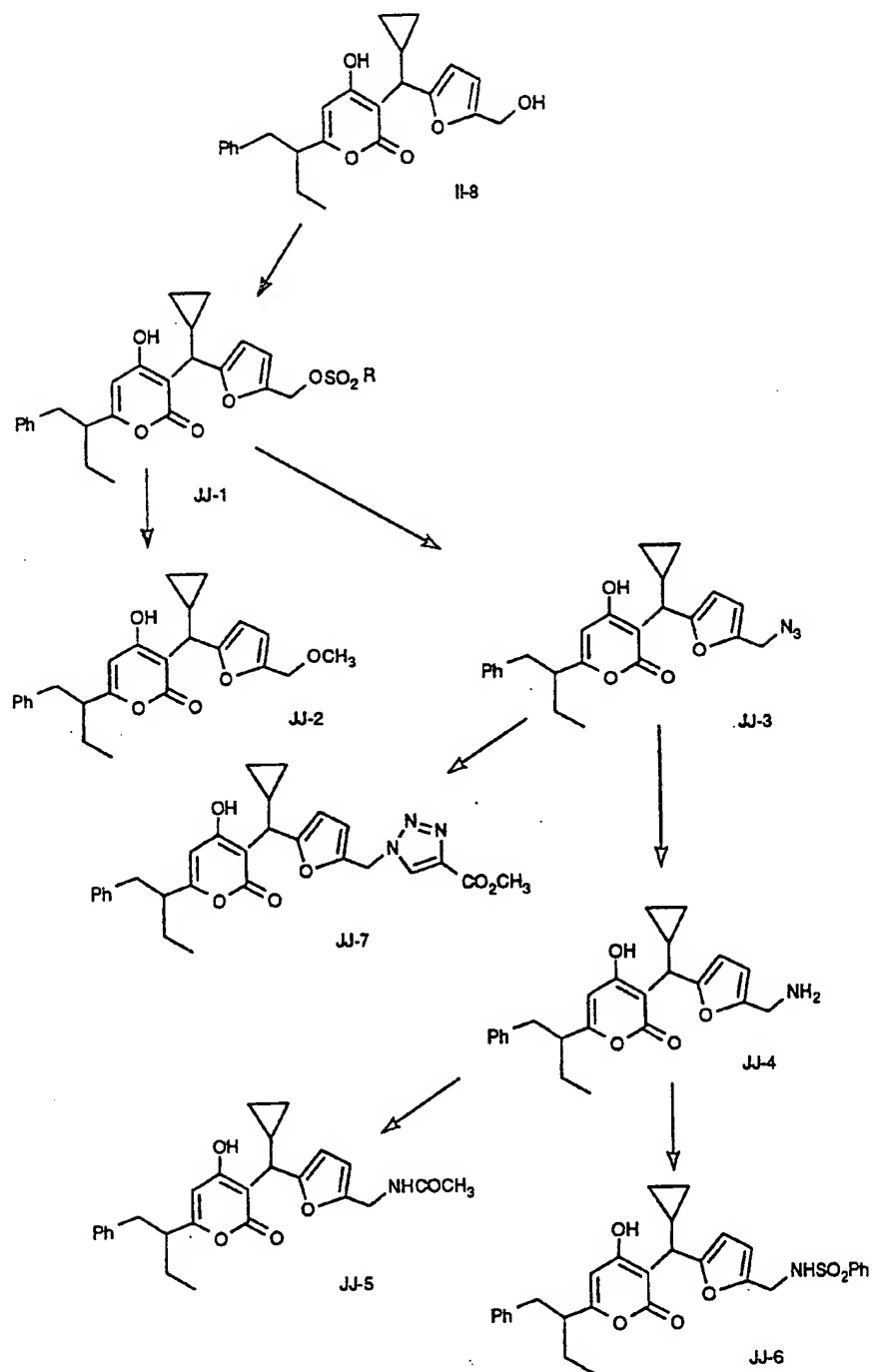
-189-

CHART II



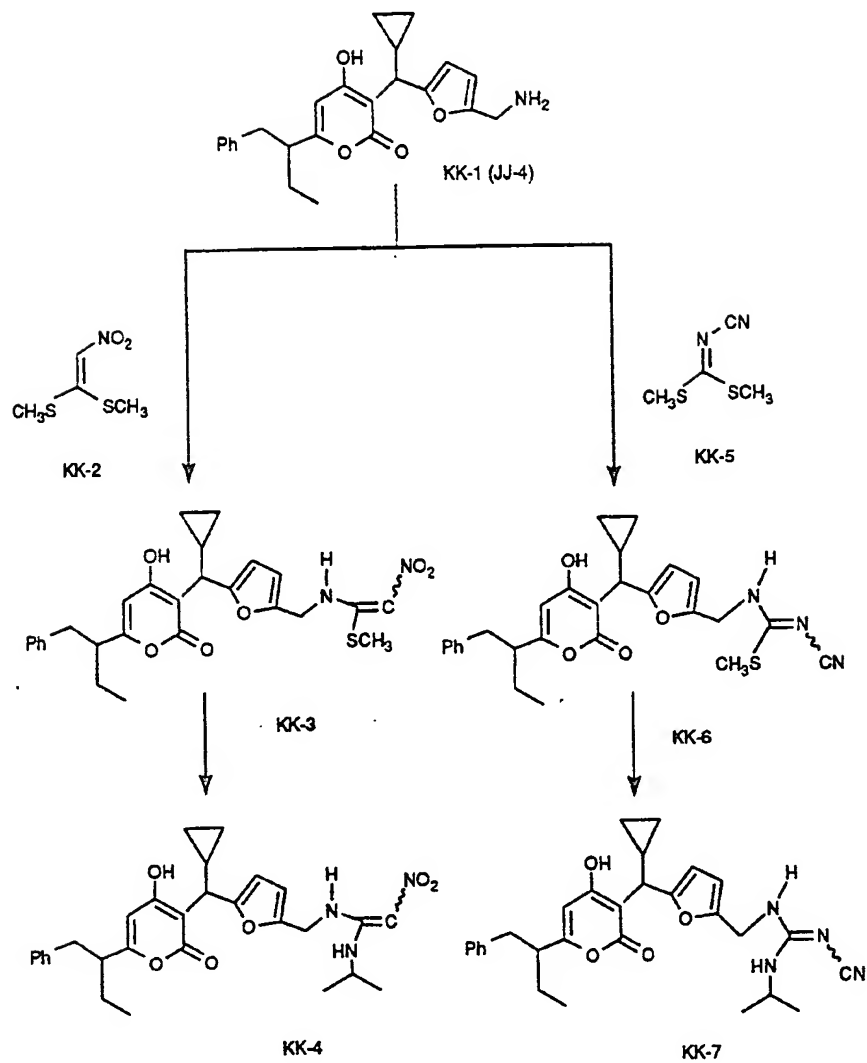
-190-

CHART JJ



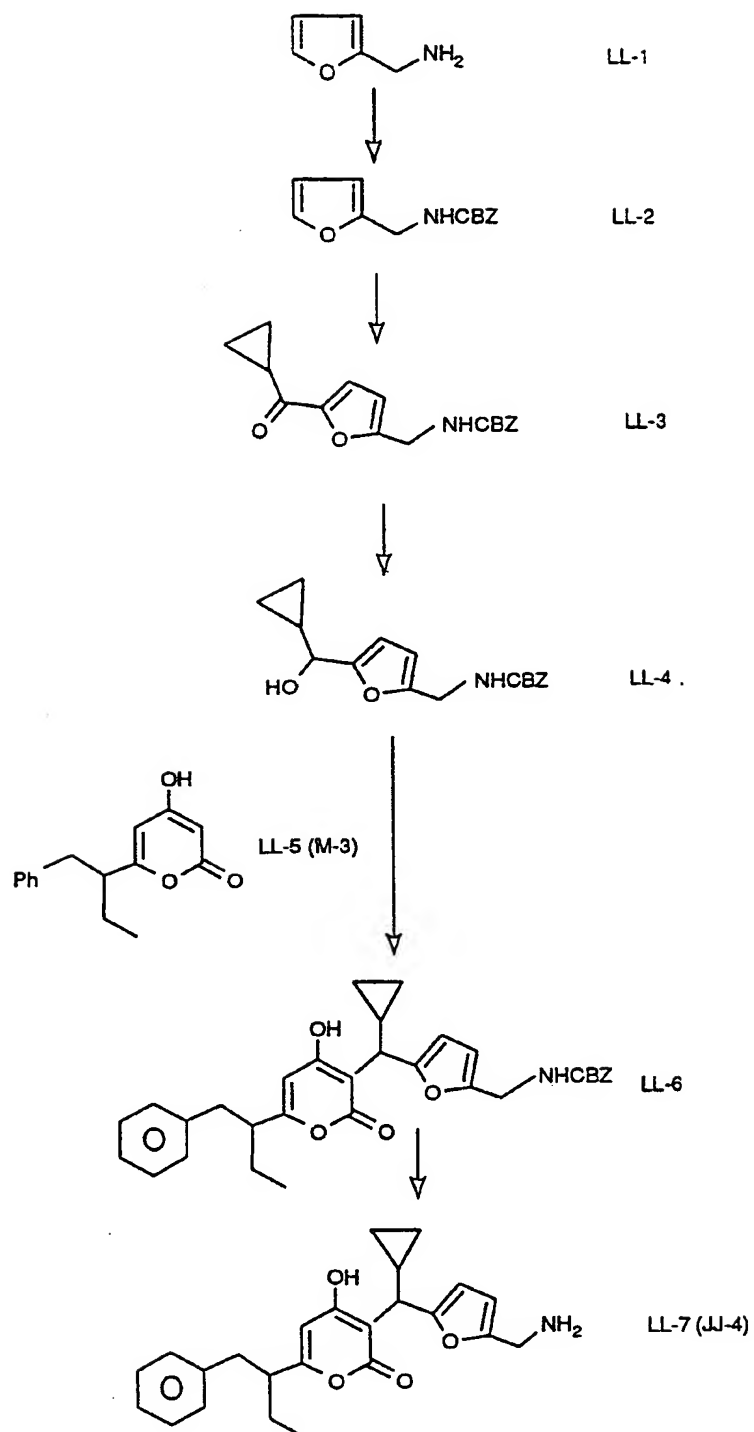
-191-

CHART KK



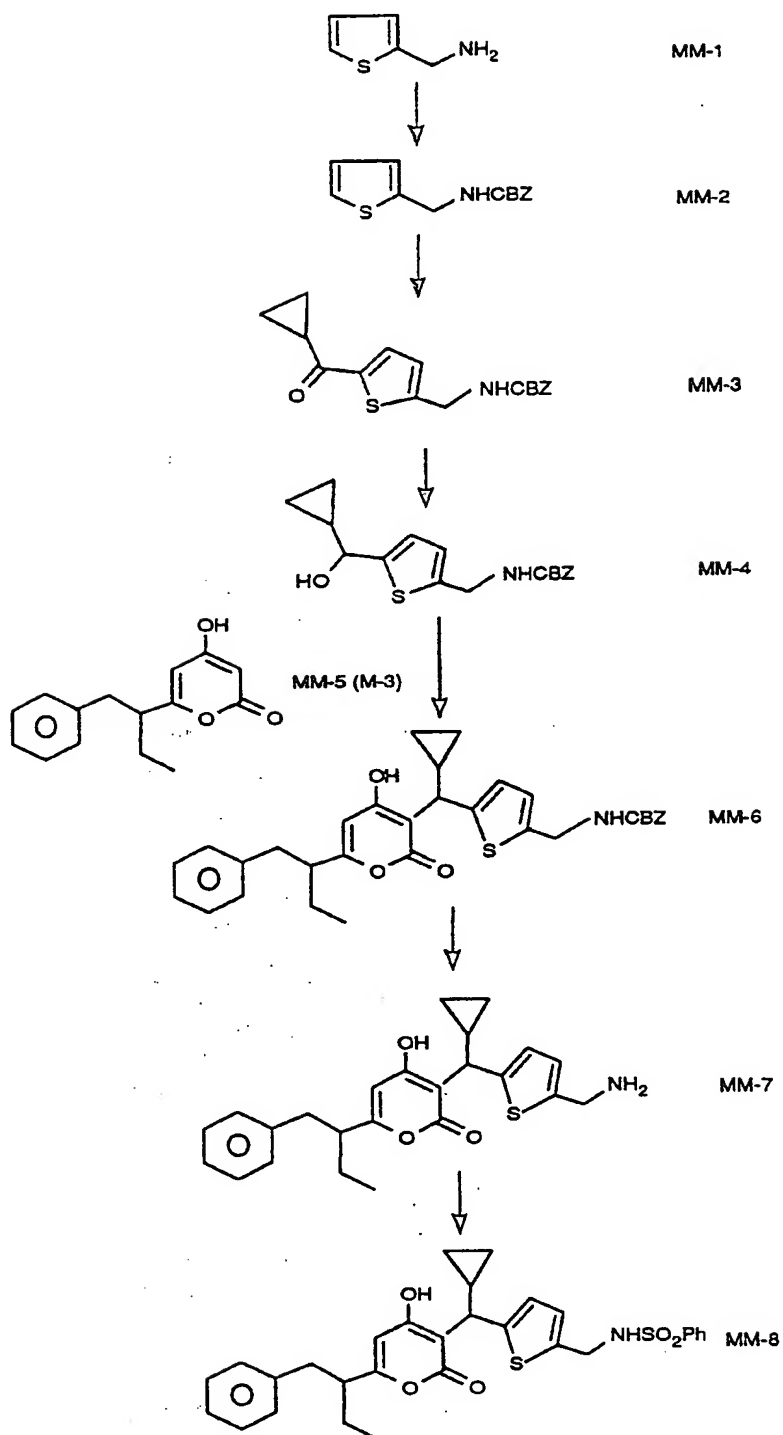
-192-

CHART LL



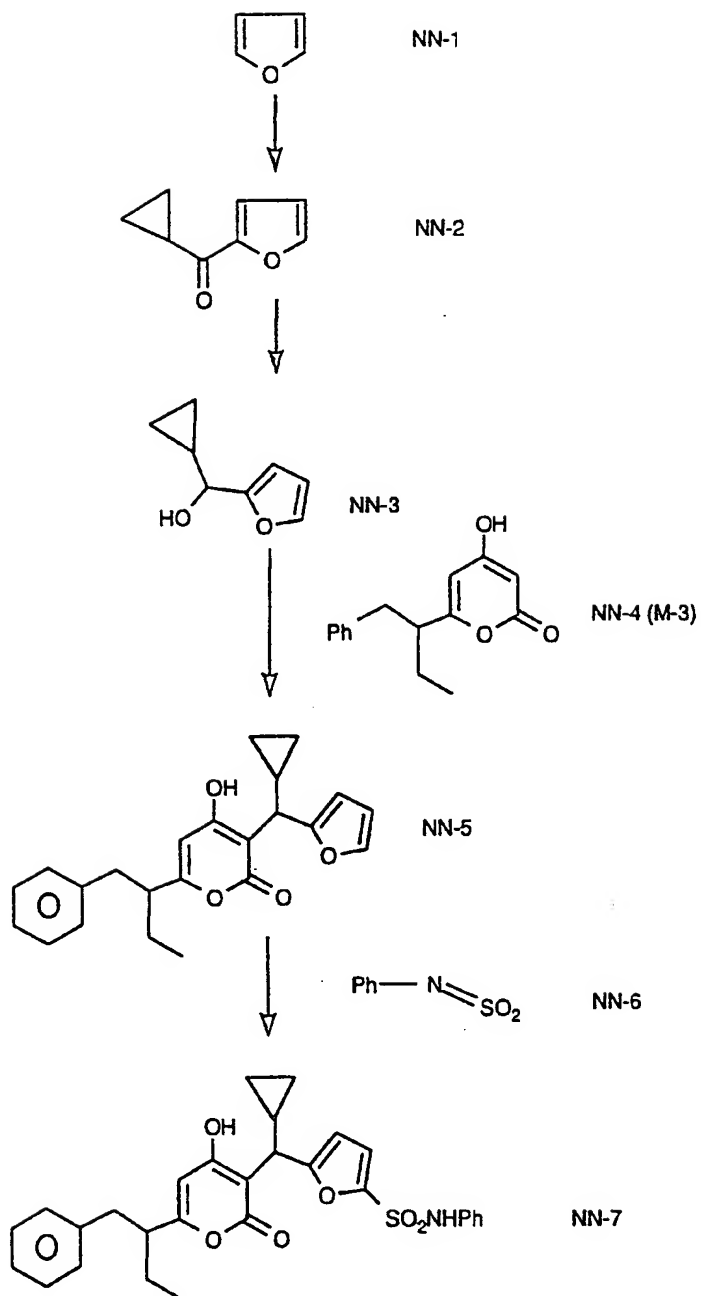
-193-

CHART MM



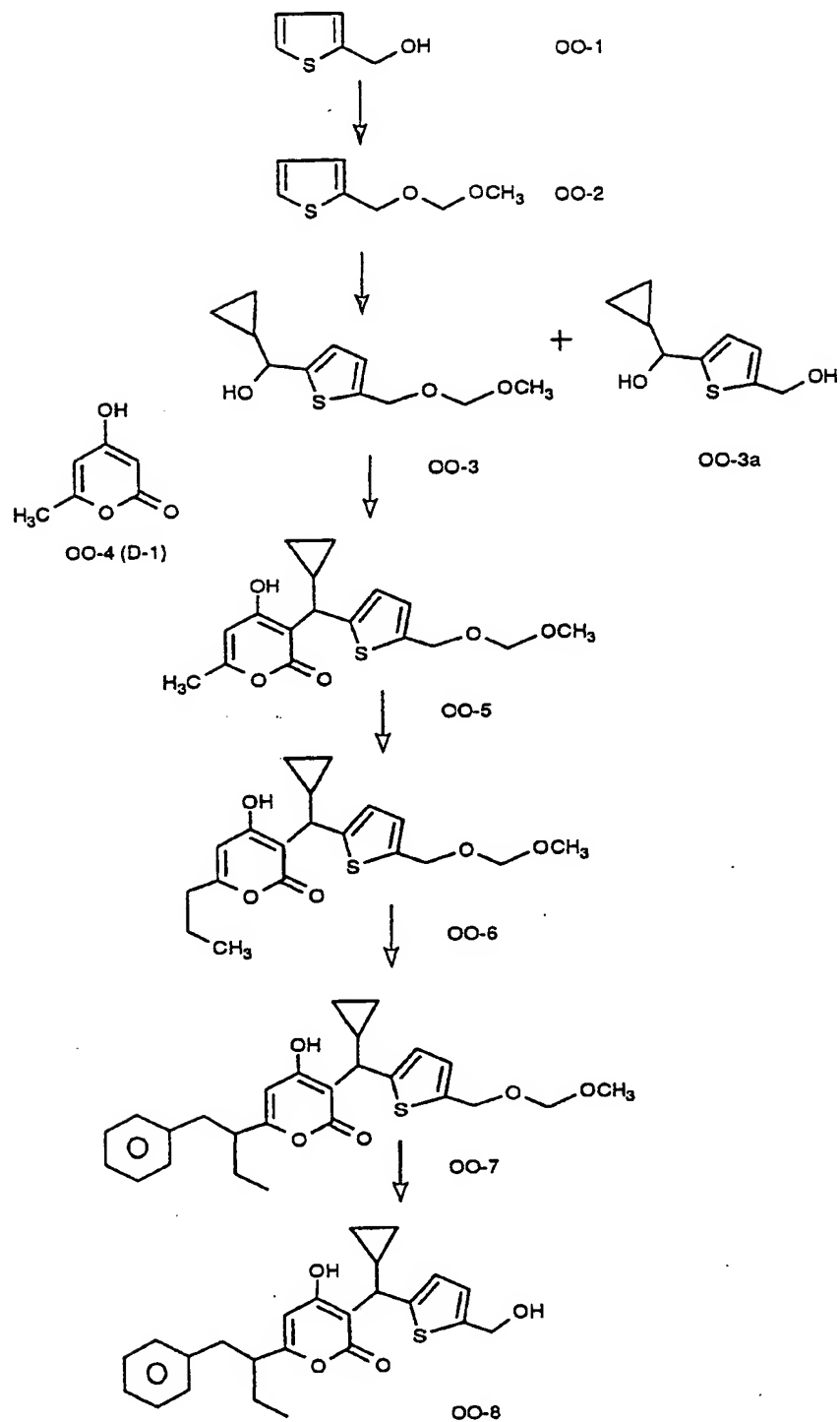
-194-

CHART NN



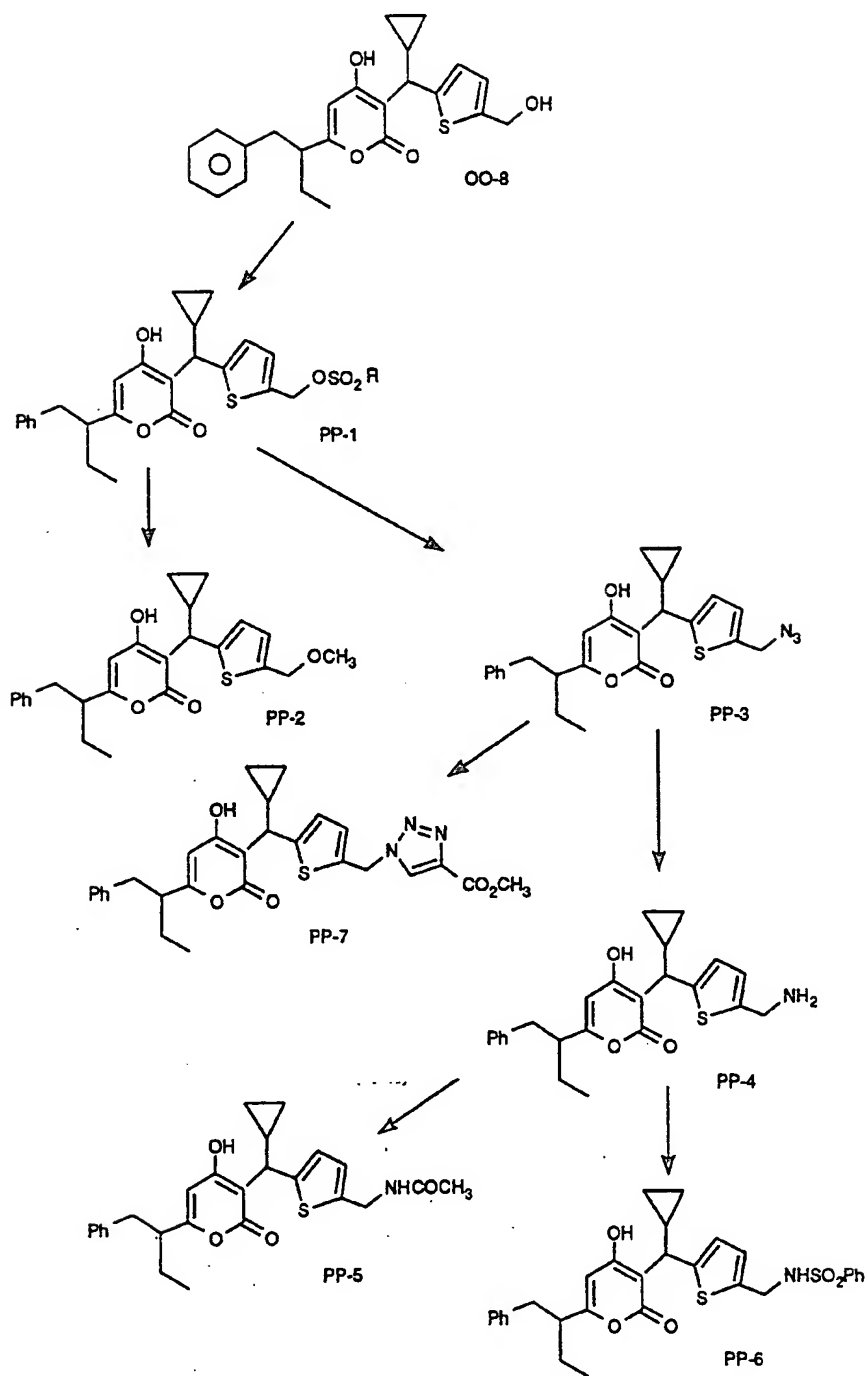
-195-

CHART OO



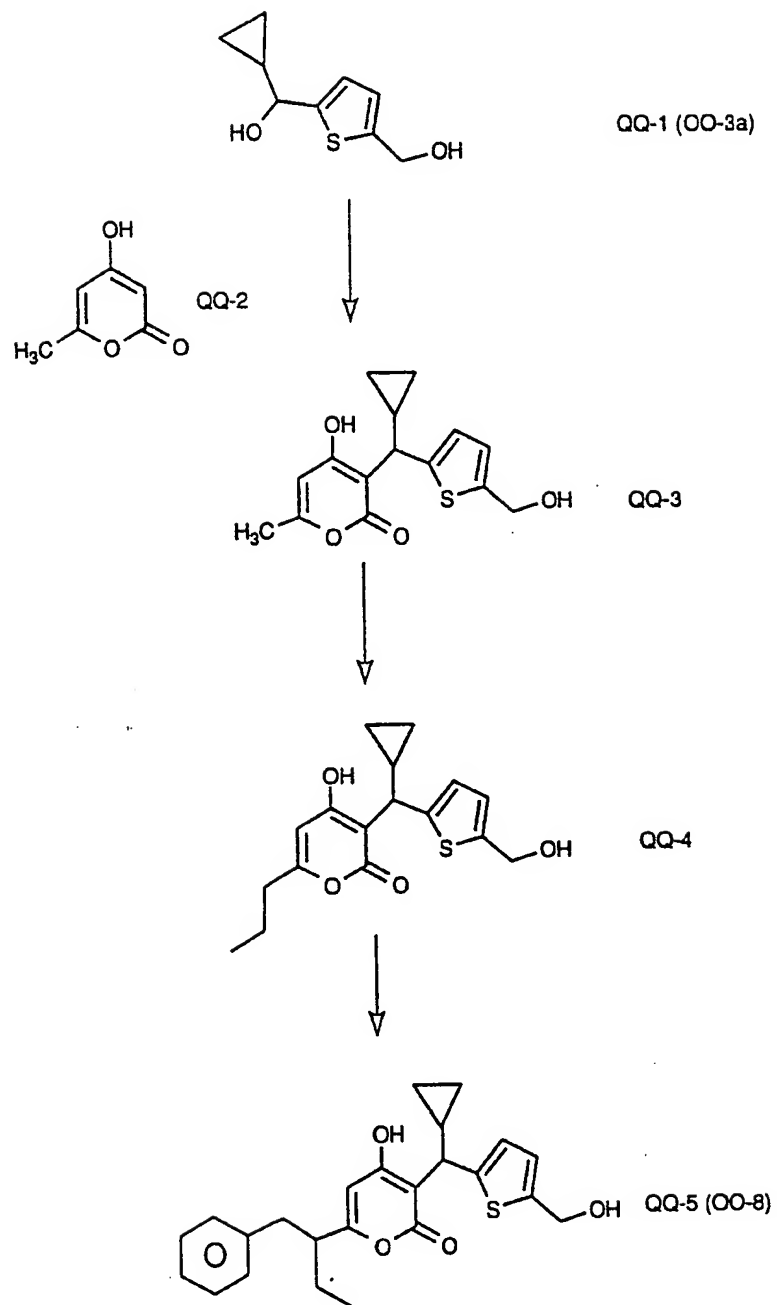
-196-

CHART PP



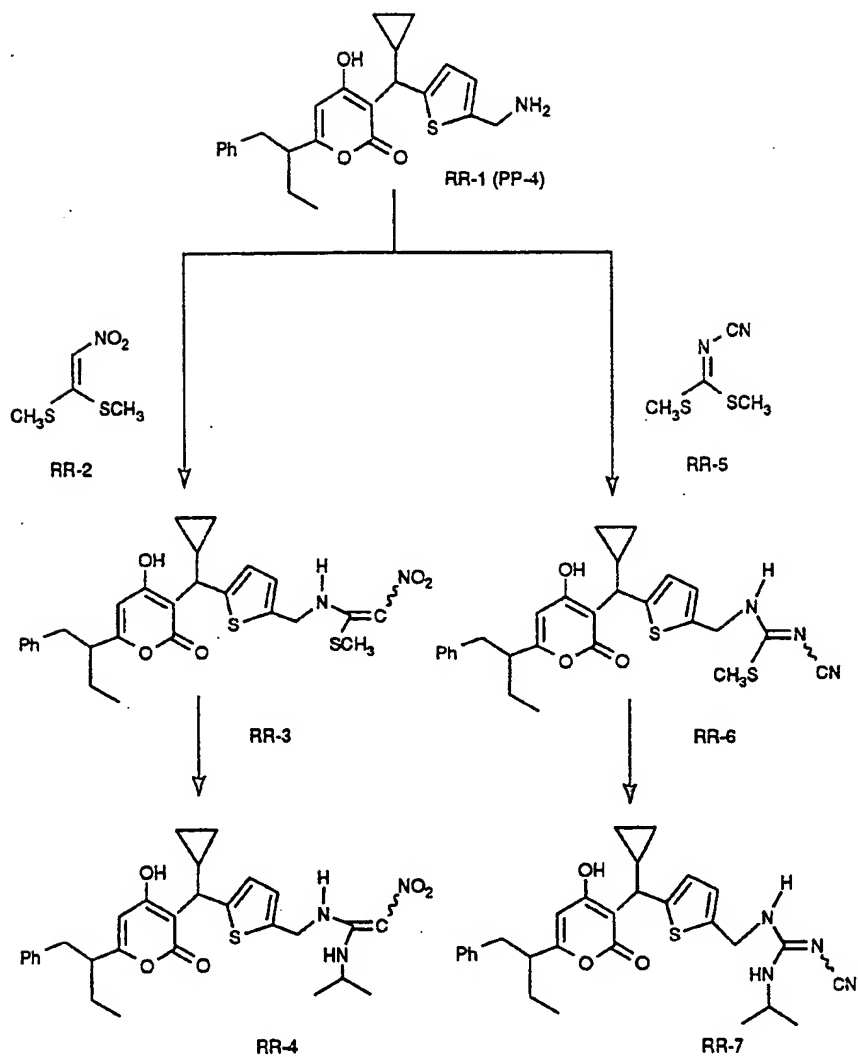
-197-

CHART QQ



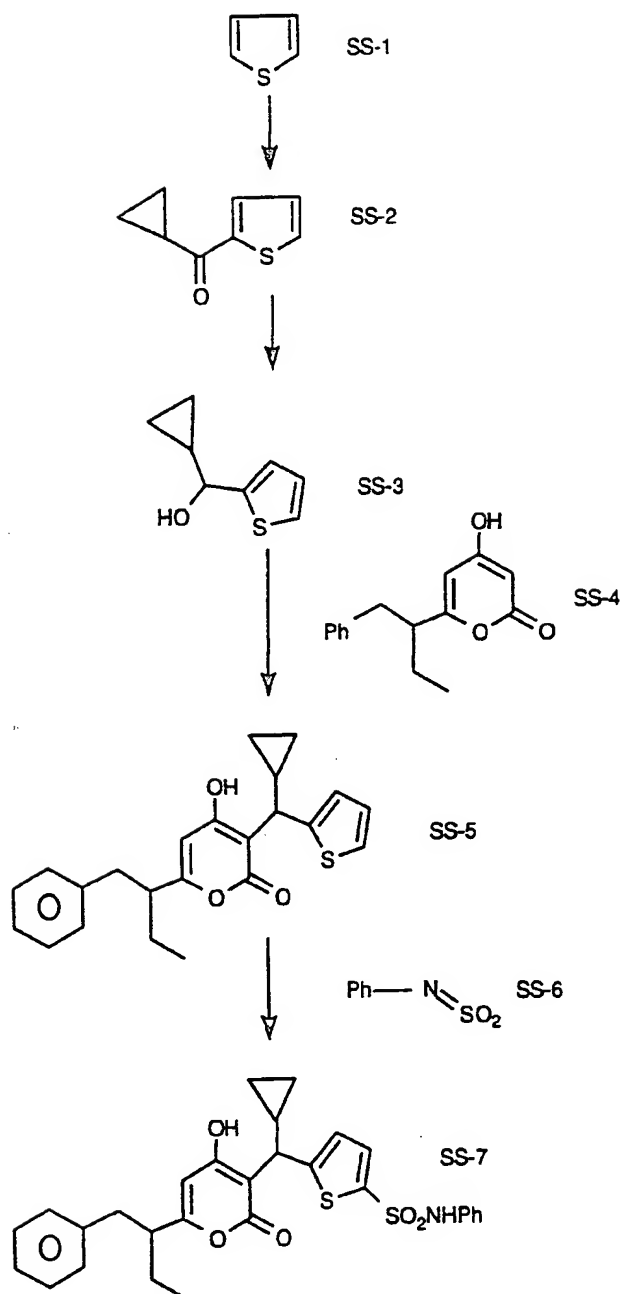
-198-

CHART RR



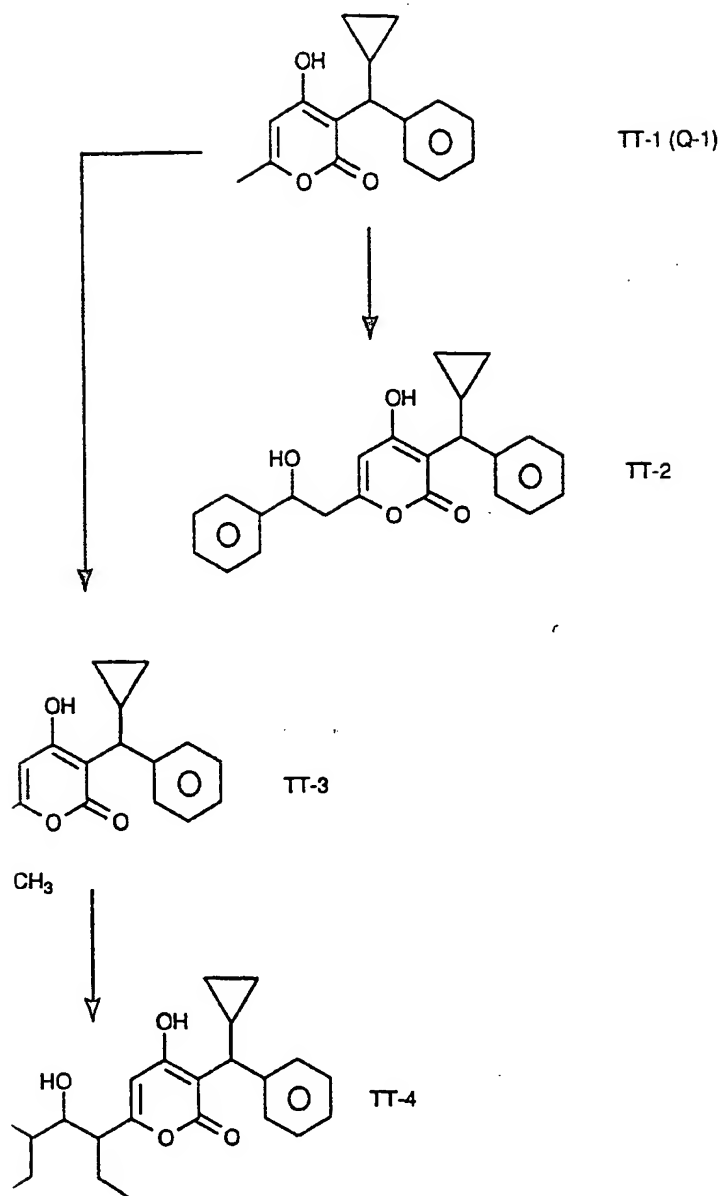
-199-

CHART SS



-200-

CHART TT



-201-

CHART UU

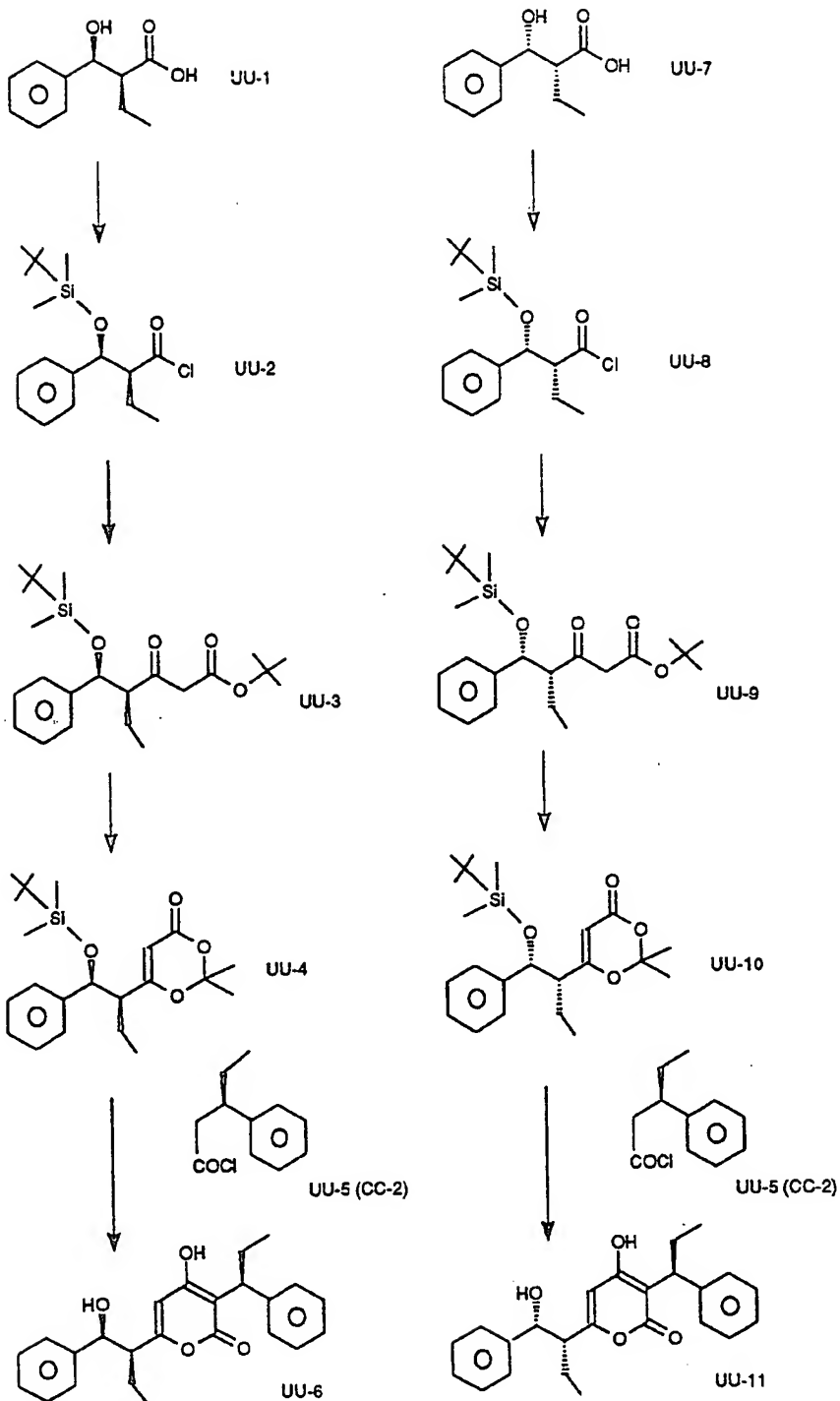
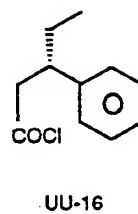
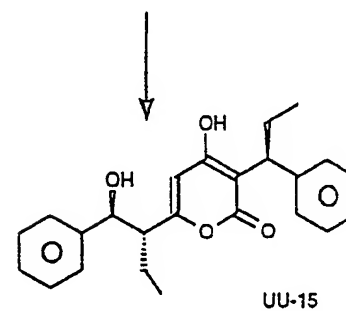
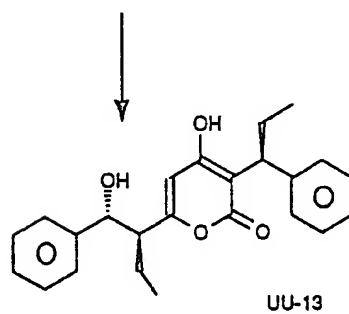
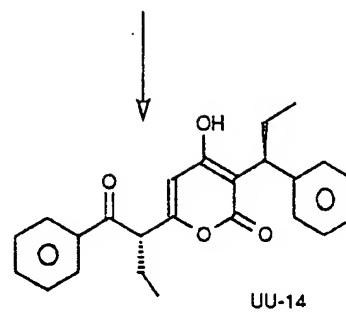
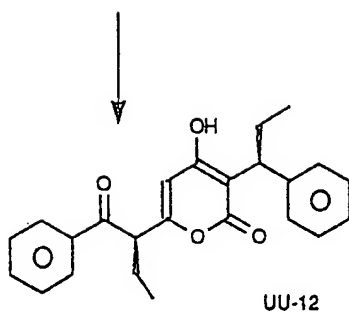
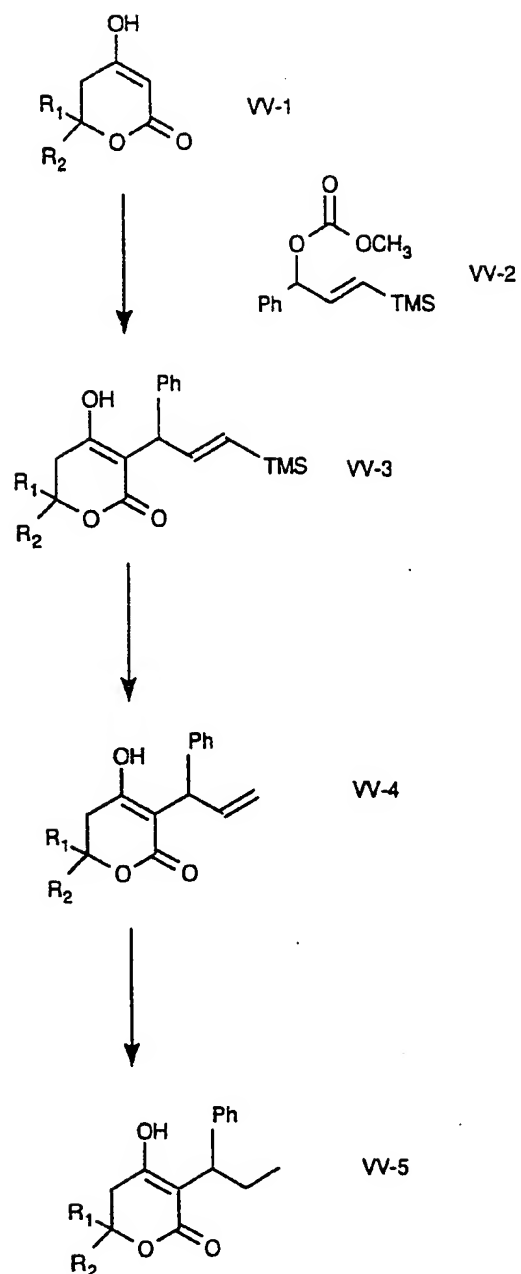


CHART UU (Continued)



-203-

CHART VV



-204-

CHART WW

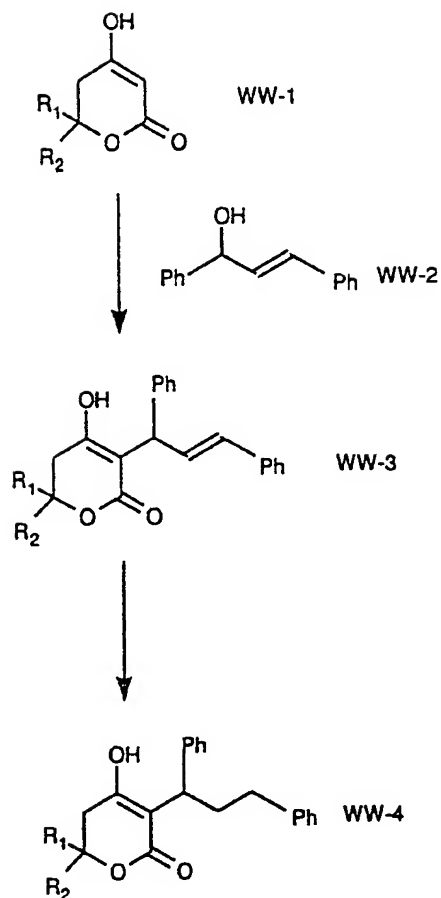
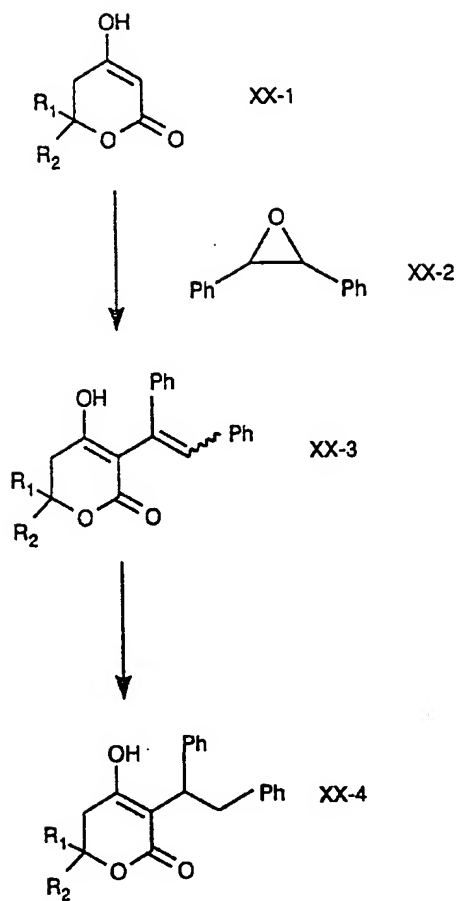
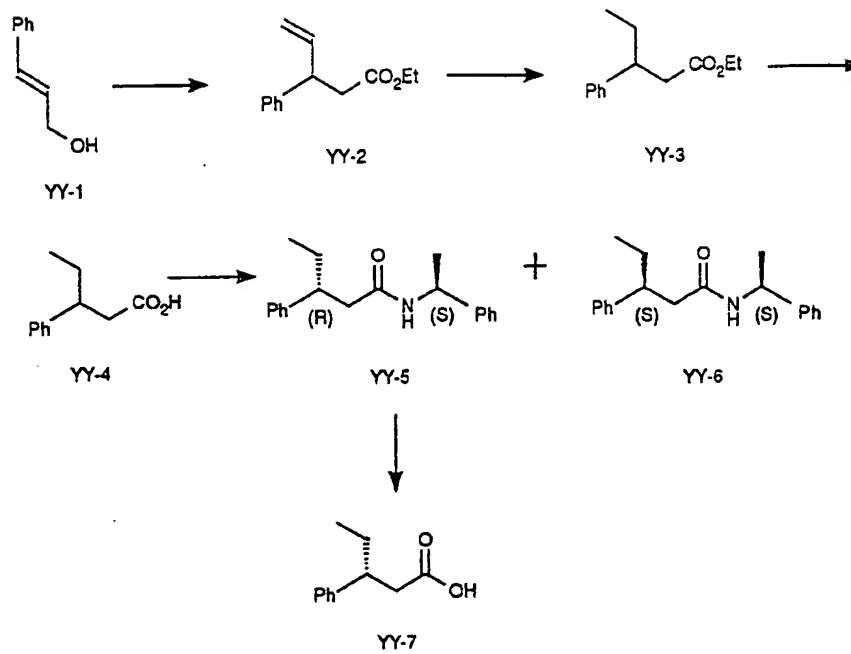


CHART XX



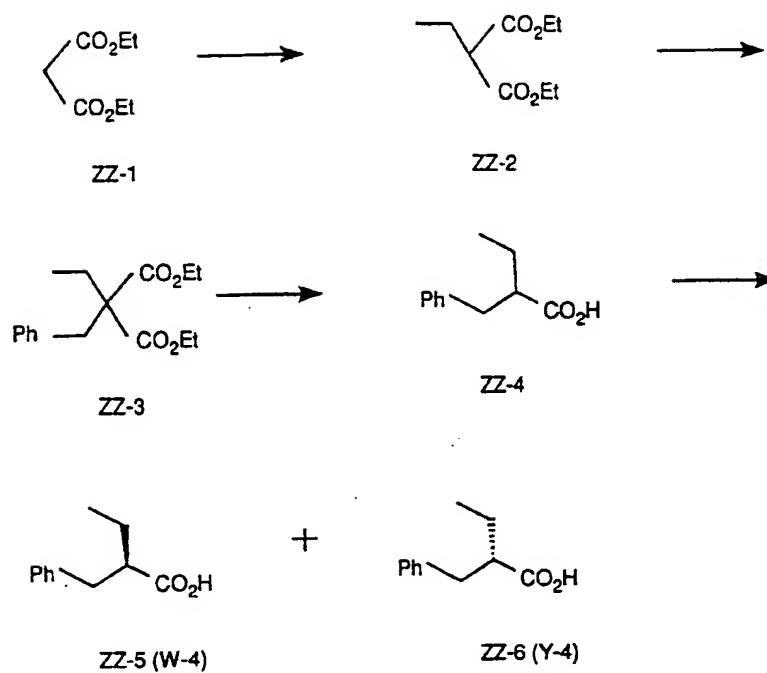
-206-

CHART YY



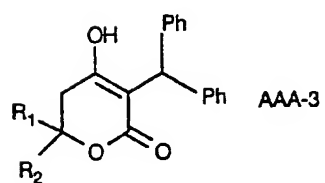
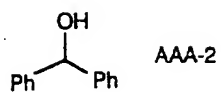
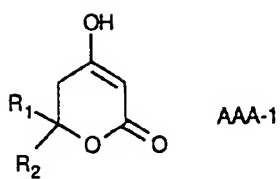
-207-

CHART ZZ



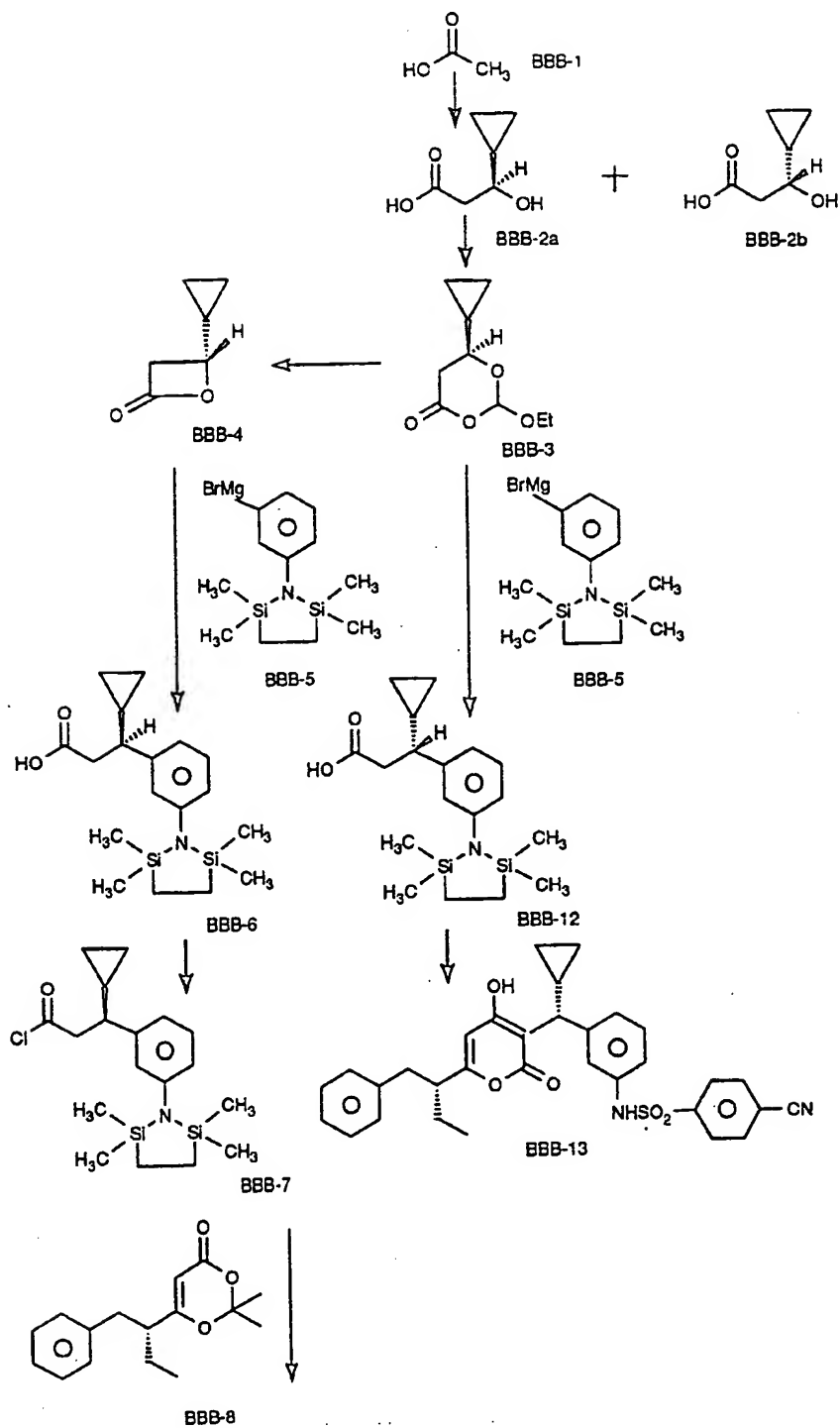
-208-

CHART AAA



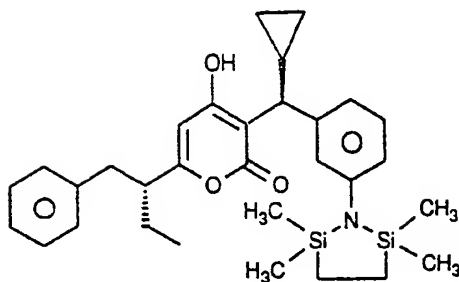
-209-

CHART BBB

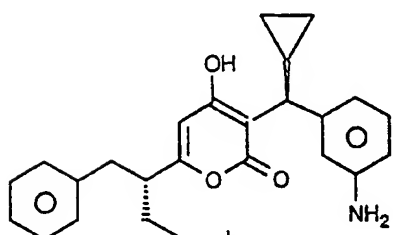


-210-

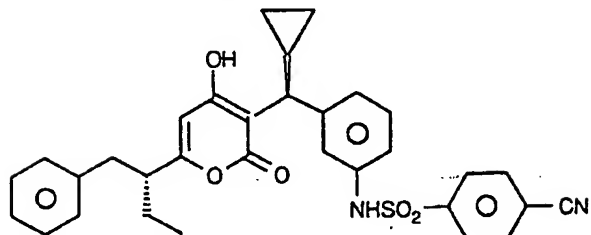
CHART BBB (Continued)



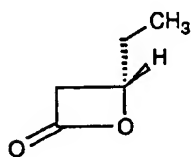
BBB-9



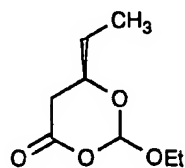
BBB-10



BBB-11



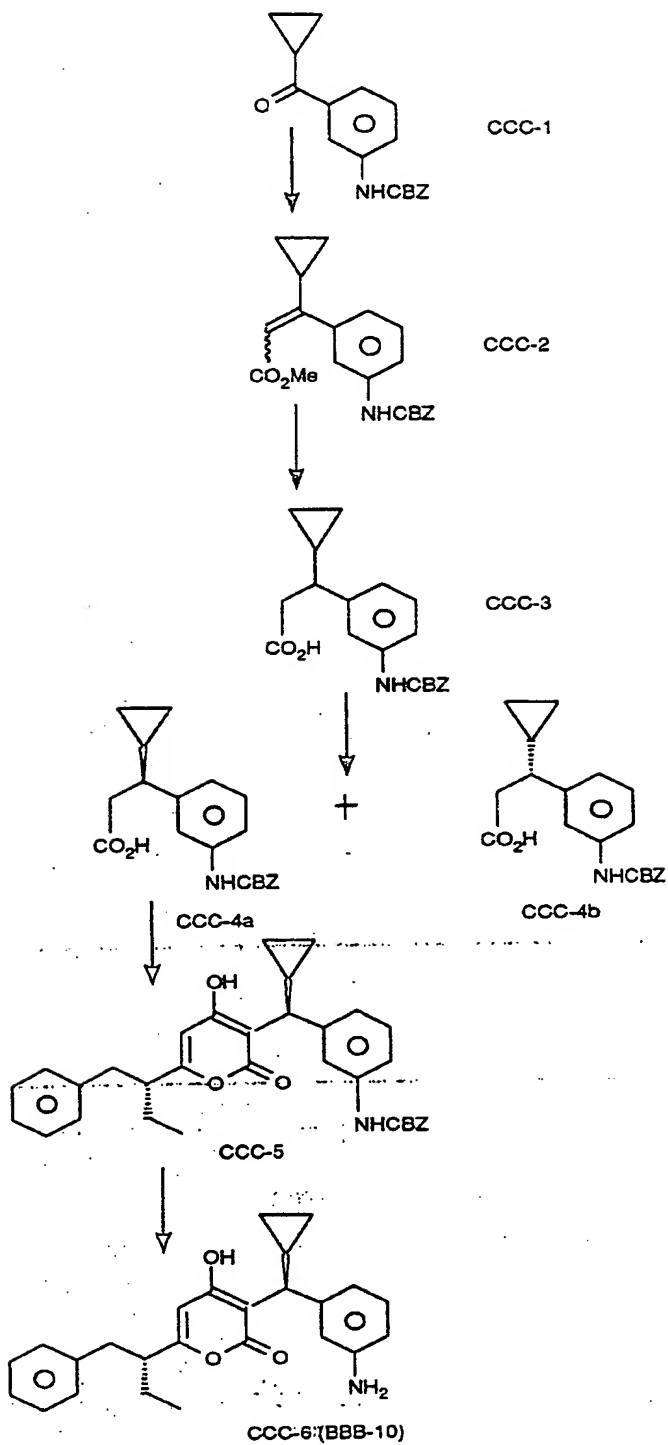
BBB-14



BBB-15

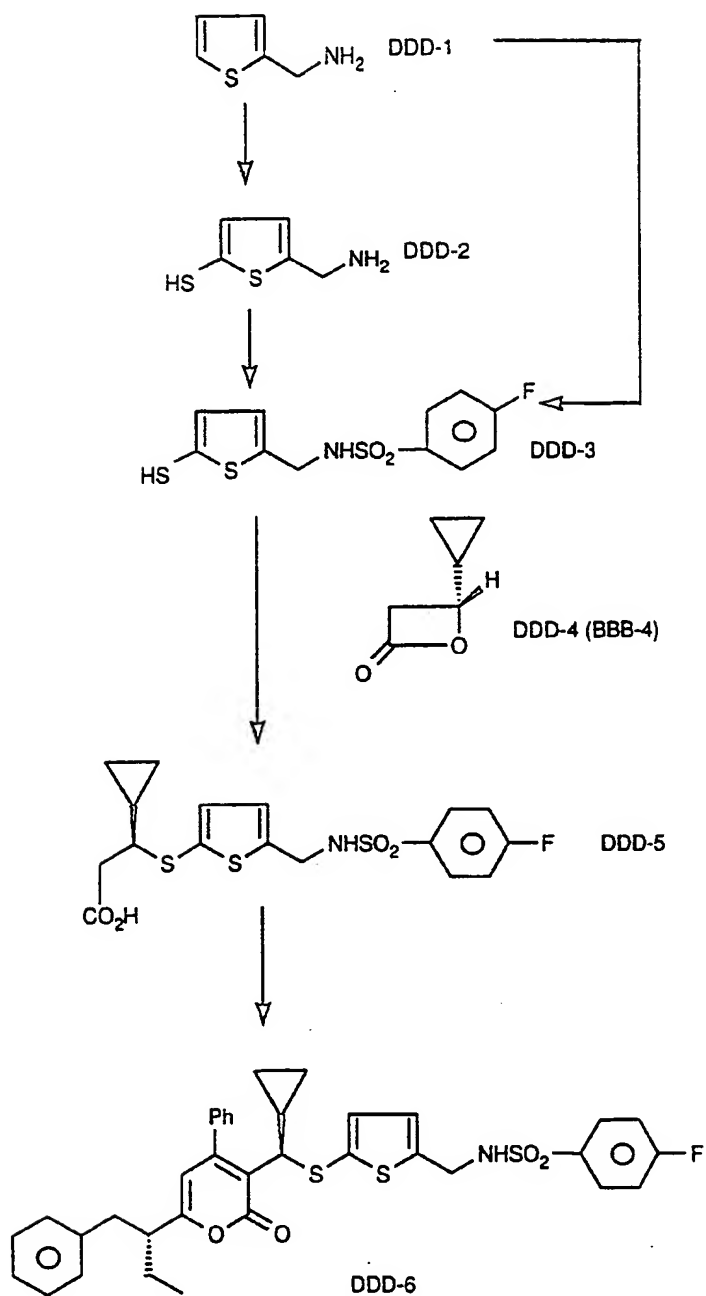
-211-

CHART CCC



-212-

CHART DDD



-213-

TABLE I

Example No.	HIV Protease FITC Assay		
	HIV-1 Dose (uM)	HIV-1 Protease % Inhib	HIV-1 Protease IC ₅₀ (uM)
3 and 5	1.000	19	
	10.000	67.4	
2	1.000	<10	
	10.000	38.69	
	100.000	74.26	
1	1.000	<10	
	10.000	45.54	
	100.000	80.02	
4	1.000	<10	
	10.000	15.76	
	100.000	51.21	
11	1.000	10.79	
	10.000	35.65	
	100.000	79.77	
PREPARATION 10	1.000	<10	
	10.000	<10	
	100.000	43.53	
6	1.000	15.58	
	10.000	39.56	
	100.000	69.68	
7	1.000	13.99	
	10.000	74.06	
	100.000	108.77	
	100.000	109	6.4000
8	1.000	15.76	
	10.000	78.96	
	100.000	96.6	
	100.000	97	3.9000

Example No.	HIV Protease FITC Assay		
	HIV-1 Dose (uM)	HIV-1 Protease % Inhib	HIV-1 Protease IC ₅₀ (uM)
5	12	1.000	17.48
		10.000	67.38
		100.000	106.62
		100.000	107
10	9	1.000	16.27
		10.000	73.49
		100.000	98.35
		100.000	19.2000
15	15	1.000	21.47
		10.000	84
		100.000	101.91
		100.000	9.7000
20	13	1.000	79.48
		10.000	92.02
		100.000	72.03
		100.000	1.3000
25	14	1.000	40.16
		10.000	90.16
		100.000	104.83
		100.000	104.83
30	10	1.000	14.18
		10.000	82.75
		100.000	104.37
		100.000	2.9000
	16	1.000	<10
		10.000	<10
		100.000	49.9
		100.000	49.9
	17	1.000	<10
		10.000	49.45
		100.000	73.62
		100.000	73.62
	18	1.000	<10
		10.000	42.06
		100.000	86.84
		100.000	86.84
	19	1.000	11
		10.000	11
		100.000	11
		100.000	11

Example No.	HIV Protease FITC Assay		
	HIV-1 Dose (uM)	HIV-1 Protease % Inhib	HIV-1 Protease IC ₅₀ (uM)
	10.000	79.27	
	100.000	84.33	
20	1.000	<10	
	10.000	<10	
	100.000	60.6	
21	1.000	17.6	
	10.000	83.66	
	100.000	109.63	9.6000
22	1.000	33.81	
	10.000	98.3	
	100.000	108.47	1.8000
23	1.000	<10	
	10.000	77.87	
	100.000	86.99	3.0000
24	1.000	<10	
	10.000	61.26	
	100.000	104.7	6.3000

TABLE II

Example No.	HIV Protease FITC Assay		
	HIV-1 Dose (uM)	HIV-1 Protease % Inhib	HIV-1 FITC Ki (nM)
5	28	1.000	<10
		10.000	15.07
		100.000	76.68
	29	1.000	<10
		10.000	<10
		100.000	32.16
10	26	1.000	38.73
		10.000	78.77
		100.000	86.28
			163
	31	1.000	18.73
		10.000	81.04
15		100.000	86.04
			610
	33	1.000	10.16
20		10.000	68.45
		100.000	80.73
	27	1.000	14.68
		10.000	41.35
		100.000	90.45
25	34	1.000	<10
		10.000	56.52
		100.000	67.88
			625
	35	1.000	23.75
		10.000	79.75
30		100.000	73.62
	32	1.000	56.11

Example No.	HIV Protease FITC Assay		
	HIV-1 Dose (uM)	HIV-1 Protease % Inhib	HIV-1 FITC Ki (nM)
	10.000	106.16	
	100.000	93.13	
			250
30	1.000	46.35	
5	10.000	86.04	
	100.000	75.74	
80	1.000	50.46	
	10.000	78.91	
	100.000	101.52	
81	1.000	41.76	
10	10.000	76.98	
	100.000	83.48	
	100.000	83.5	
		<10	
41	1.000	21.22	
15	10.000	65.89	
	100.000	80.92	
40	1.000	37.25	
20	10.000	79.47	
	100.000	79.95	
82	1.000	19.84	
	10.000	90.86	
	100.000	106.06	
83	1.000	10.51	
25	10.000	72.03	
	100.000	93.47	
84	1.000	54.77	
	10.000	90.97	
30	100.000	120.09	

Example No.	HIV Protease FITC Assay		
	HIV-1 Dose (uM)	HIV-1 Protease % Inhib	HIV-1 FITC Ki (nM)
5	100.000	100	
	85	1.000	11.61
	10.000	76.97	
	100.000	92.14	
	86	1.000	58.14
	10.000	83.02	
10	100.000	55.3	
	87	1.000	17.78
	10.000	83.79	
	100.000	90.15	
	88	1.000	46.18
	10.000	60.78	
15	100.000	95.13	
	89	1.000	<10
	10.000	69.98	
	100.000	83.95	
		<10	
	90	1.000	61.19
20	10.000	95.14	
	100.000	95.86	
	100.000	96	
	91	1.000	<10
	10.000	27.79	
	100.000	61.98	
25	92	1.000	38.29
	10.000	80.92	
	100.000	87.1	
	93	1.000	31.75
	10.000	72.62	
	100.000	79.29	
30			

Example No.	HIV Protease FITC Assay		
	HIV-1 Dose (uM)	HIV-1 Protease % Inhib	HIV-1 FITC Ki (nM)
		<10	
	1.000	13.28	
	10.000	67.65	
	100.000	59.48	
5	1.000	15.47	
	10.000	71.27	
	100.000	67.68	
94	1.000	<10	
	10.000	24.98	
10	100.000	52.36	
95	1.000	<10	
	10.000	33.64	
	100.000	41	
42	1.000	19.68	
15	10.000	74.68	
	100.000	104.53	
			520
96	1.000	27.93	
	10.000	77.03	
20	100.000	90.52	
			1400
43	1.000	44.64	
	10.000	89.44	
	100.000	97.34	
25			460
97	1.000	75.88	
	10.000	99.59	
	100.000	109.6	
			100
30	98	1.000	50.77

-220-

Sample No.	HIV Protease FITC Assay		
	HIV-1 Dose (uM)	HIV-1 Protease % Inhib	HIV-1 FITC Ki (nM)
	10.000	93.45	
	100.000	109.88	
99	1.000	71.49	
	10.000	99.63	
	100.000	90.67	
100	1.000	38.34	
	10.000	94.63	
	100.000	104.11	
			480
101	1.000	52.16	
	10.000	78.81	
	100.000	97.94	
102	1.000	33.8	
	10.000	62.17	
	100.000	105.05	
			1520
103	1.000	26.56	
	10.000	31.32	
	100.000	82.97	
104	1.000	50.02	
	10.000	73.15	
	100.000	87.33	
105	0.410	14.28	
	1.230	38.87	
	3.700	75.26	
	11.000	102.73	
	33.000	109.96	
	100.000	108.22	
			458
106	0.410	57.42	

Example No.	HIV Protease FITC Assay		
	HIV-1 Dose (uM)	HIV-1 Protease % Inhib	HIV-1 FITC Ki (nM)
5	1.230	82.12	
	3.700	100.83	
	11.000	110.66	
	33.000	115.33	
	100.000	118.6	
			58
10	77	0.410	69.4
		1.230	86.94
		3.700	101.15
		11.000	108.7
		33.000	107.73
		100.000	110.05
			75
15	107	0.410	49.97
		1.230	80.33
		3.700	100.43
		11.000	103.08
		33.000	108.64
		100.000	109.5
20			41
	108	0.410	<10
		1.230	20.42
		3.700	46.9
		11.000	76.71
25		33.000	84.85
		100.000	117.93
			607
30	109	0.410	22.21
		1.230	51.84
		3.700	78.91

-222-

Example No.	HIV Protease FITC Assay		
	HIV-1 Dose (uM)	HIV-1 Protease % Inhib	HIV-1 FITC Ki (nM)
5	11.000	105.59	
	33.000	105.32	
	100.000	107.78	
			203
	0.410	<10	
10	1.230	16.07	
	3.700	43.16	
	11.000	71.15	
	33.000	88.58	
	100.000	84.27	
15	0.410	50.49	
	1.230	68.86	
	3.700	93.25	
	11.000	101.27	
	33.000	107.36	
20	100.000	105.88	
			196
	0.410	41.68	
	1.230	66.21	
	3.700	92.21	
25	11.000	102.83	
	33.000	101.94	
	100.000	109.16	
			255
	0.410	<10	
30	1.230	<10	
	3.700	10.39	
	11.000	18.91	
	33.000	37.1	
	100.000	46.47	

-223-

Example No.	HIV Protease FITC Assay		
	HIV-1 Dose (μ M)	HIV-1 Protease % inhib	HIV-1 FITC Ki (nM)
5	44	0.410	<10
		1.230	24.85
		3.700	57.29
		11.000	84.35
		33.000	105.8
		100.000	113.76
			1836
10	45	0.410	79.27
		1.230	94.42
		3.700	101.48
		11.000	103.08
		33.000	114.2
		100.000	116.38
			53
15	46	0.410	29.2
		1.230	65.04
		3.700	91.56
		11.000	94.16
		33.000	103.45
		100.000	115.43
			313
20	47	0.410	<10
		1.230	19.35
		3.700	49.97
		11.000	73.15
		33.000	91.27
		100.000	107.49
			505
25	48	0.410	<10
		1.230	<10

Example No.	HIV Protease FITC Assay		
	HIV-1 Dose (uM)	HIV-1 Protease % Inhib	HIV-1 FITC Ki (nM)
5	3.700	<10	
	11.000	<10	
	33.000	31.26	
	100.000	61.6	
	0.410	<10	
10	1.230	24.58	
	3.700	52.34	
	11.000	80	
	33.000	93.7	
	100.000	98.29	
15			425
	0.410	<10	
	1.230	22.12	
	3.700	55.49	
	11.000	80.54	
20	33.000	96.03	
	100.000	105.94	
			353
	0.410	<10	
	1.230	<10	
25	3.700	23.36	
	11.000	50.72	
	33.000	69.96	
	100.000	83.71	
	0.410	<10	
30	1.230	13.69	
	3.700	43.37	
	11.000	73.66	
	33.000	77.2	
	100.000	87.48	

-225-

Example No.	HIV Protease FITC Assay		
	HIV-1 Dose (uM)	HIV-1 Protease % Inhib	HIV-1 FITC Ki (nM)
5	52	0.410	66.58
		1.230	86.23
		3.700	105.75
		11.000	112.38
		33.000	115.67
		100.000	113.27
			43
10	53	0.410	19.39
		1.230	47.54
		3.700	86.03
		11.000	102.07
		33.000	117.33
		100.000	120.08
			220
15	54	0.410	85.01
		1.230	95.84
		3.700	109.19
		11.000	113.2
		33.000	117.22
		100.000	100.24
			72
20	55	0.410	<10
		1.230	24.14
		3.700	59.64
		11.000	92.14
		33.000	89.59
		100.000	101.96
			578
25	56	0.410	92.59
		1.230	97.74

-226-

Example No.	HIV Protease FITC Assay		
	HIV-1 Dose (uM)	HIV-1 Protease % Inhib	HIV-1 FITC Ki (nM)
5	3.700	106.13	
	11.000	116.72	
	33.000	118.66	
	100.000	109.06	
			37
10	57	0.410	76.69
		1.230	89.41
		3.700	103.06
		11.000	108.08
		33.000	113.58
15		100.000	116.44
			63
	58	0.410	74.53
		1.230	91.09
		3.700	107.15
20		11.000	108.05
		33.000	114.54
		100.000	110.32
			48
	59	0.410	64.18
25		1.230	81.25
		3.700	103.59
		11.000	102.37
		33.000	100.67
		100.000	104.82
30			58
	60	0.410	63.22
		1.230	86.73
		3.700	105.84
		11.000	112.61

Example No.	HIV Protease FITC Assay		
	HIV-1 Dose (uM)	HIV-1 Protease % Inhib	HIV-1 FITC Ki (nM)
	33.000	111.41	
	100.000	122.68	
			46
61	0.410	100.27	
	1.230	100.59	
	3.700	107.72	
	11.000	111.3	
	33.000	110.87	
	100.000	103.18	
			13
62	0.410	85.69	
	1.230	95.75	
	3.700	107.61	
	11.000	115.62	
	33.000	112.66	
	100.000	123.1	
			74
37	0.410	90.19	
	1.230	101.45	
	3.700	101.87	
	11.000	114.95	
	33.000	113.2	
	100.000	106.9	
			41
63	0.410	68.46	
	1.230	95.78	
	3.700	100.57	
	11.000	110.35	
	33.000	111.63	
	100.000	117.37	

Example No.	HIV Protease FITC Assay		
	HIV-1 Dose (uM)	HIV-1 Protease % Inhib	HIV-1 FITC Ki (nM)
			79
5	38	0.123	<10
		0.370	<10
		1.100	<10
		3.300	26.72
		10.000	58.44
10		30.000	69.94
	79	0.123	39.93
		0.370	76.71
		1.100	106.03
		3.300	110.68
15		10.000	121.73
		30.000	117.33
			33
	64	0.123	13.71
		0.370	53.93
20		1.100	87.67
		3.300	102.83
		10.000	109.39
		30.000	118.67
			44
25	65	0.123	<10
		0.370	27.98
		1.100	71.22
		3.300	93.23
		10.000	107.28
30		30.000	121.71
			141
	113	0.410	<10
		1.230	15.27

-229-

Example No.	HIV Protease FITC Assay		
	HIV-1 Dose (uM)	HIV-1 Protease % Inhib	HIV-1 FITC Ki (nM)
5	3.700	42.78	
	11.000	79.74	
	33.000	100.7	
	100.000	107.1	
			2565
10	114	0.410	<10
		1.230	<10
		3.700	25.79
		11.000	63.5
		33.000	67.45
15		100.000	55.36
			4287
	115	0.410	<10
		1.230	27.11
		3.700	56.89
20		11.000	91.53
		33.000	102.62
		100.000	94.81
			1159
	120	0.123	<10
25		0.370	<10
		1.100	10.14
		3.300	26.24
		10.000	46.37
		30.000	60.1
30	121	0.123	<10
		0.370	<10
		1.100	<10
		3.300	10.76
		10.000	40.24

-230-

Example No.	HIV Protease FITC Assay		
	HIV-1 Dose (uM)	HIV-1 Protease % Inhib	HIV-1 FITC Ki (nM)
	30.000	68.46	
116	0.123	<10	
	0.370	<10	
	1.100	<10	
5	3.300	31.07	
	10.000	62.03	
	30.000	89.89	
117	0.123	<10	
	0.370	<10	
10	1.100	16.99	
	3.300	51.16	
	10.000	87.01	
	30.000	100.57	
118	0.123	<10	
15	0.370	<10	
	1.100	19.98	
	3.300	52.4	
	10.000	83.91	
	30.000	101.62	
20	0.123	<10	
	0.370	<10	
	1.100	<10	
	3.300	<10	
	10.000	20.66	
25	30.000	60.3	
39	0.123	<10	
	0.370	24.81	
	1.100	60.63	
	3.300	86.31	
30	10.000	91.85	

Example No.	HIV Protease FITC Assay		
	HIV-1 Dose (uM)	HIV-1 Protease % Inhib	HIV-1 FITC Ki (nM)
	30.000	94.46	
			96
66	0.123	<10	
	0.370	36.03	
	1.100	75.26	
	3.300	99.39	
	10.000	101.85	
	30.000	108.42	
			53
67	0.123	<10	
	0.370	32.64	
	1.100	72.63	
	3.300	92.3	
	10.000	106.66	
	30.000	118.42	
			84
68	0.123	<10	
	0.370	15.1	
	1.100	47.69	
	3.300	80.33	
	10.000	98.74	
	30.000	112.34	
			132
69	0.123	<10	
	0.370	<10	
	1.100	13.88	
	3.300	42.07	
	10.000	75.2	
	30.000	98.51	
70	0.123	<10	

-232-

Example No.	HIV Protease FITC Assay		
	HIV-1 Dose (uM)	HIV-1 Protease % Inhib	HIV-1 FITC Ki (nM)
5	0.370	38.34	
	1.100	67.26	
	3.300	88.89	
	10.000	92.8	
	30.000	98.6	
			64
10	71	0.123	11.63
		0.370	46.27
		1.100	74.95
		3.300	83.97
		10.000	95.27
		30.000	96.36
15			54
	72	0.123	34.98
		0.370	68.38
		1.100	90.73
		3.300	98.67
		10.000	93.87
20		30.000	97.65
			31
	73	0.123	<10
		0.370	<10
		1.100	<10
		3.300	<10
25		10.000	28.87
		30.000	61.35
	74	0.123	<10
		0.370	17.54
		1.100	53.43
		3.300	81.38
30			

-233-

Example No.	HIV Protease FITC Assay		
	HIV-1 Dose (uM)	HIV-1 Protease % Inhib	HIV-1 FITC Ki (nM)
5	10.000	96.71	
	30.000	106.49	186
	75	0.123	11.46
	0.370	33.84	
	1.100	65.96	
	3.300	86.61	
	10.000	98.45	
	30.000	104	127
10	76	0.123	24.98
	0.370	54.05	
	1.100	82.41	
	3.300	98.87	
	10.000	101.5	
	30.000	105.25	
15	123	0.123	<10
	0.370	<10	
	1.100	<10	
	3.300	14.75	
	10.000	39.64	
	30.000	72.02	
20	131	0.123	<10
	0.370	<10	
	1.100	<10	
	3.300	<10	
	10.000	13.24	
	30.000	45.94	
25	132	0.123	<10
	0.370	<10	
	1.100	29.05	
	3.300	70.25	
30			

-234-

Example No.	HIV Protease FITC Assay		
	HIV-1 Dose (uM)	HIV-1 Protease % Inhib	HIV-1 FITC Ki (nM)
5	10.000	87.6	
	30.000	109.94	
	133	0.123	20.56
	0.370	49.57	
	1.100	74.26	
	3.300	95.91	
10	10.000	110.1	
	30.000	102.05	40
	134	0.123	21.1
	0.370	57.53	
	1.100	83.08	
	3.300	99.66	
15	10.000	110.57	
	30.000	105.9	24
	135	0.123	12.44
	0.370	26.49	
	1.100	65.56	
	3.300	87.92	
20	10.000	103.26	
	30.000	99.86	45
	136	0.123	<10
	0.370	24.5	
	1.100	62.42	
	3.300	91.34	
25	10.000	99.09	
	30.000	99.7	52.000
	137	0.123	<10
	0.370	<10	
	1.100	23	
	3.300	57.23	
30			

-235-

Example No.	HIV Protease FITC Assay		
	HIV-1 Dose (uM)	HIV-1 Protease % Inhib	HIV-1 FITC Ki (nM)
	10.000	80.2	
	30.000	79.72	
138	0.123	<10	
	0.370	<10	
	1.100	24.76	
	3.300	63.92	
	10.000	83.26	
	30.000	81.12	
139	0.123	<10	
	0.370	<10	
	1.100	<10	
	3.300	27.91	
	10.000	58	
	30.000	67.12	
140	0.123	<10	
	0.370	10.53	
	1.100	38.65	
	3.300	70.24	
	10.000	81.62	
	30.000	77.13	
141	0.123	<10	
	0.370	<10	
	1.100	<10	
	3.300	<10	
	10.000	11.25	
	30.000	17	
142	0.123	<10	
	0.370	<10	
	1.100	26.95	
	3.300	64.27	

-236-

Example No.	HIV Protease FITC Assay		
	HIV-1 Dose (uM)	HIV-1 Protease % Inhib	HIV-1 FITC Ki (nM)
5	10.000	88.74	
	30.000	103.62	
	143	0.123	<10
	0.370	<10	
	1.100	25.08	
	3.300	57.87	
10	10.000	83.07	
	30.000	93.79	
	144	0.123	<10
	0.370	<10	
	1.100	<10	
	3.300	<10	
15	10.000	<10	
	30.000	22.69	
	145	0.123	<10
	0.370	<10	
	1.100	<10	
	3.300	26.6	
20	10.000	59.67	
	30.000	84.39	
	124	0.123	<10
	0.370	<10	
	1.100	<10	
	3.300	27.51	
25	10.000	53.41	
	30.000	64.85	
	125	0.123	<10
	0.370	<10	
	1.100	15.4	
	3.300	45.71	
30			

Example No.	HIV Protease FITC Assay		
	HIV-1 Dose (uM)	HIV-1 Protease % Inhib	HIV-1 FITC Ki (nM)
5	10.000	71.05	
	30.000	89.67	
	0.123	<10	
	0.370	<10	
	1.100	13.18	
10	3.300	42.87	
	10.000	66.76	
	30.000	80.96	
	0.123	<10	
	0.370	14.43	
15	1.100	38.37	
	3.300	65.63	
	10.000	98.91	
	30.000	102.21	
	0.123	<10	
20	0.370	<10	
	1.100	18.53	
	3.300	46.84	
	10.000	79.82	
	30.000	95.72	
25	0.123	<10	
	0.370	<10	
	1.100	43.51	
	3.300	67.07	
	10.000	80.7	
30	30.000	83.4	
	0.123	<10	
	0.370	<10	
	1.100	<10	
	3.300	<10	

Example No.	HIV Protease FITC Assay		
	HIV-1 Dose (μ M)	HIV-1 Protease % Inhib	HIV-1 FITC Ki (nM)
5	10.000	<10	
	30.000	13.11	
	0.123	36.44	
	0.370	73.64	
	1.100	82.74	
	3.300	87.71	
10	10.000	91.19	
	30.000	95.17	
	0.123	<10	
	0.370	<10	
	1.100	28.87	
	3.300	52.59	
15	10.000	78.14	
	30.000	89.24	
	100.000	114.29	
	0.123	<10	
	0.370	22.39	
	1.100	52.05	
20	3.300	80.26	
	10.000	91.92	
	30.000	89.74	
	100.000	130.07	161.000
	0.123	<10	
	0.370	19.73	
25	1.100	46.86	
	3.300	73.49	
	10.000	98.5	
	30.000	103.16	
	100.000	117.12	267.000
	0.123	<10	
30	150		

Example No.	HIV Protease FITC Assay		
	HIV-1 Dose (uM)	HIV-1 Protease % Inhib	HIV-1 FITC Ki (nM)
5	0.370	13.26	
	1.100	25.37	
	3.300	54.08	
	10.000	75.25	
	30.000	90.99	
	100.000	112.67	
10	151	0.123	<10
		0.370	<10
		1.100	19.07
		3.300	39.8
		10.000	70.1
		30.000	88.38
15		100.000	112.67
	152	0.123	<10
		0.370	<10
		1.100	26.39
		3.300	48.81
		10.000	77.57
20		30.000	90.55
		100.000	109.97
	153	0.123	<10
		0.370	17.68
		1.100	40.3
		3.300	69
25		10.000	88.59
		30.000	99.69
		100.000	120.02
	154	0.123	21.87
		0.370	57.26
		1.100	84.08
30			

-240-

Example No.	HIV Protease FITC Assay		
	HIV-1 Dose (uM)	HIV-1 Protease % Inhib	HIV-1 FITC Ki (nM)
	3.300	86.73	
	10.000	98.1	
	30.000	92.91	39.000
155	0.123	27.61	
	0.370	45.98	
	1.100	79.88	
	3.300	92.84	
	10.000	97.23	
	30.000	93.47	
	100.000	111.15	66.000
156	0.123	<10	
	0.370	24.24	
	1.100	64.39	
	3.300	82.64	
	10.000	87.29	
	30.000	92.32	65.000
157	0.123	<10	
	0.370	17.62	
	1.100	42.2	
	3.300	68.96	
	10.000	83.45	
	30.000	84.94	
158	0.123	15.74	
	0.370	44.21	
	1.100	70.49	
	3.300	86.96	
	10.000	100.25	
	30.000	96.08	
	100.000	115.03	55.000
159	0.123	<10	

Example No.	HIV Protease FITC Assay		
	HIV-1 Dose (μ M)	HIV-1 Protease % Inhib	HIV-1 FITC Ki (nM)
5	0.370	20.61	
	1.100	56.35	
	3.300	76.22	
	10.000	92.26	
	30.000	95.07	207.000
10	160	0.123	<10
	0.370	12.21	
	1.100	39.39	
	3.300	78.2	
	10.000	89.7	
15		30.000	92.07
	161	0.123	<10
	0.370	<10	
	1.100	41.75	
	3.300	78.05	
20		10.000	96.51
		30.000	105.27
	162	0.123	<10
	0.370	<10	
	1.100	<10	
25		3.300	34.36
		10.000	52.01
		30.000	72.27
	163	0.123	<10
	0.370	30.76	
30		1.100	65.56
		3.300	88.65
		10.000	100.71
		30.000	98.41
	164	0.123	<10
			172.000

Example No.	HIV Protease FITC Assay		
	HIV-1 Dose (uM)	HIV-1 Protease % Inhib	HIV-1 FITC Ki (nM)
5	0.370	16.52	
	1.100	50.05	
	3.300	68.8	
	10.000	84.77	
	30.000	88.25	185.000
165	0.123	<10	
10	0.370	10.46	
	1.100	32.93	
	3.300	60	
	10.000	80.65	
	30.000	94.09	
166	0.123	<10	
15	0.370	<10	
	1.100	<10	
	3.300	39.83	
	10.000	62.33	
	30.000	80.88	
20	100.000	97.8	
	0.123	<10	
	0.370	<10	
	1.100	18.41	
	3.300	37.12	
25	10.000	60.4	
	30.000	81.1	
	0.123	<10	
	0.370	<10	
	1.100	<10	
30	3.300	10.43	
	10.000	43.37	
	30.000	48.01	

-243-

Example No.	HIV Protease FITC Assay		
	HIV-1 Dose (uM)	HIV-1 Protease % Inhib	HIV-1 FITC Ki (nM)
5	169	0.123	<10
		0.370	<10
		1.100	<10
		3.300	<10
		10.000	33.2
		30.000	54.77
10	170	0.123	<10
		0.370	29.65
		1.100	62.15
		3.300	86.65
		10.000	95.12
		30.000	93
15	171	0.123	11.75
		0.370	39.5
		1.100	68.91
		3.300	82.22
		10.000	96.79
		30.000	94.56
20	172	0.123	<10
		0.370	<10
		1.100	11.68
		3.300	29.52
		10.000	56.83
		30.000	60.65
25	173	0.123	<10
		0.370	<10
		3.300	<10
		10.000	39.17
		30.000	58.78
	174	0.123	23.48

-244-

Example No.	HIV Protease FITC Assay		
	HIV-1 Dose (uM)	HIV-1 Protease % Inhib	HIV-1 FITC Ki (nM)
	0.370	52.75	
	1.100	81.81	
	3.300	102.28	
	10.000	109.78	
5	30.000	105.99	16.000
175	0.123	19.72	
	0.370	46.67	
	1.100	78.8	
	3.300	99.32	
10	10.000	106.63	
	30.000	104.64	35.000
176	0.123	<10	
	0.370	<10	
	1.100	28.85	
15	3.300	62.26	
	10.000	88.68	
	30.000	100.54	
177	0.123	<10	
	0.370	19.71	
20	1.100	48.17	
	3.300	74.17	
	10.000	89.26	
	30.000	94.96	
178	0.123	21.61	
25	0.370	61.86	
	1.100	83.11	
	3.300	95.49	
	10.000	103.79	
	30.000	106.84	17.400
30	179	0.123	23.72

Example No.	HIV Protease FITC Assay		
	HIV-1 Dose (uM)	HIV-1 Protease % Inhib	HIV-1 FITC Ki (nM)
	0.370	61.9	
	1.100	77.89	
	3.300	94.44	
	10.000	95.1	
5	30.000	102.08	40.000
180	0.123	31.96	
	0.370	55.93	
	1.100	80.55	
	3.300	91.92	
10	10.000	99.51	
	30.000	97.97	23.300
181	0.123	32.59	
	0.370	64.5	
	1.100	82.44	
15	3.300	95.26	
	10.000	100.69	
	30.000	95.51	18.900
182	0.123	<10	
	0.370	15.01	
20	1.100	45.74	
	3.300	71.91	
	10.000	94.9	
	30.000	96.49	
183	0.123	<10	
25	0.370	11.86	
	1.100	28.24	
	3.300	60.64	
	10.000	88.89	
	30.000	90.81	
30	184	0.123	65.05

Example No.	HIV Protease FITC Assay		
	HIV-1 Dose (uM)	HIV-1 Protease % Inhib	HIV-1 FITC Ki (nM)
5	0.370	87.05	
	1.100	94.47	
	3.300	98.98	
	10.000	101.68	
	30.000	102.3	5.700
10	185	0.123	40.51
	0.370	71.44	
	1.100	89.06	
	3.300	95.89	
	10.000	103.11	
15	30.000	92.87	
	186	0.123	<10
	0.370	<10	
	1.100	<10	
	3.300	11	
20	10.000	41.6	
	30.000	61.57	22.400
	25		41.000
	122	100.000	26
	243	0.123	<10
25	0.370	36.19	
	1.100	70.5	
	3.300	94.71	
	10.000	105.14	
	30.000	102.44	69.000
30	232	0.123	10.57
	0.370	36.97	
	1.100	73.74	
	3.300	93.56	
	10.000	103.56	

Example No.	HIV Protease FITC Assay		
	HIV-1 Dose (uM)	HIV-1 Protease % Inhib	HIV-1 FITC Ki (nM)
	30.000	98.87	76.000
233	0.123	<10	
	0.370	28.94	
	1.100	64.9	
	3.300	83.12	
	10.000	93.73	
	30.000	59.36	24.800
234	0.123	<10	
	0.370	33.42	
	1.100	61.65	
	3.300	81.06	
	10.000	83	
	30.000	71.12	39.400
235	0.123	<10	
	0.370	13.7	
	1.100	33.22	
	3.300	61.61	
	10.000	73.28	
	30.000	80.14	
212	0.123	<10	
	0.370	<10	
	1.100	17.78	
	3.300	43.17	
	10.000	67.06	
	30.000	69.63	
213	0.123	<10	
	0.370	12.05	
	1.100	29.96	
	3.300	55.36	
	10.000	83.7	

Example No.	HIV Protease FITC Assay		
	HIV-1 Dose (uM)	HIV-1 Protease % Inhib	HIV-1 FITC Ki (nM)
5	30.000	85.76	
	221 0.123	43.14	
	0.370	72.11	
	1.100	87.27	
	3.300	102.12	
10	10.000	108.14	
	30.000	100.56	14.600
	222 0.123	18.96	
	0.370	51.72	
	1.100	75.75	
15	3.300	91.01	
	10.000	98.28	
	30.000	95.85	18.500
	223 0.123	<10	
	0.370	<10	
20	1.100	13.93	
	3.300	33.88	
	10.000	59.68	
	30.000	65.06	
	224 0.123	46.89	
25	0.370	76.9	
	1.100	99.6	
	3.300	97.12	
	10.000	109.97	
	30.000	104.76	14.700
30	236 0.123	<10	
	0.370	<10	
	1.100	26.03	
	3.300	54.13	
	10.000	75.82	

-249-

Example No.	HIV Protease FITC Assay		
	HIV-1 Dose (uM)	HIV-1 Protease % Inhib	HIV-1 FITC Ki (nM)
5	30.000	78.74	
	237	0.123	<10
	0.370	10.21	
	1.100	32.02	
	3.300	60.21	
	10.000	80.87	
10	30.000	78.17	
	225	0.123	<10
	0.370	<10	
	1.100	<10	
	3.300	21.01	
	10.000	30.58	
15	30.000	35.45	
	226	0.123	73.44
	0.370	93.91	
	1.100	106.24	
	3.300	104.34	
	10.000	100.97	
20	30.000	98.32	4.000
	227	0.123	<10
	0.370	19.58	
	1.100	49.16	
	3.300	80.24	
	10.000	89.81	
25	30.000	85.44	
	214	0.123	<10
	0.370	<10	
	1.100	32.03	
	3.300	65.96	
	10.000	79.53	
30			

-250-

Example No.	HIV Protease FITC Assay		
	HIV-1 Dose (uM)	HIV-1 Protease % Inhib	HIV-1 FITC Ki (nM)
5	30.000	85.99	
	215	0.123	<10
	0.370	<10	
	1.100	<10	
	3.300	16.14	
10	10.000	23.11	
	30.000	28.84	
	238	0.123	<10
	0.370	20.5	
	1.100	52.77	
15	3.300	75.64	
	10.000	81	
	30.000	87.08	163.000
	239	0.123	<10
	0.370	35.83	
20	1.100	63.94	
	3.300	79.84	
	10.000	91.05	
	30.000	85.69	99.000
	216	0.123	<10
25	0.370	29.76	
	1.100	61.07	
	3.300	85.6	
	10.000	91.5	
	30.000	90.47	122.000
30	244	0.123	20.72
	0.370	57.94	
	1.100	81.9	
	3.300	90.61	
	10.000	102.94	

-251-

Example No.	HIV Protease FITC Assay		
	HIV-1 Dose (uM)	HIV-1 Protease % Inhib	HIV-1 FITC Ki (nM)
	30.000	99.42	15.400
245	0.123	25.87	
	0.370	58.02	
	1.100	83.28	
	3.300	90.32	
	10.000	96.93	
	30.000	94.08	20.600
246	0.123	24.72	
	0.370	60.06	
	1.100	79.88	
	3.300	92.35	
	10.000	92.69	
	30.000	93.33	21.600
247	0.123	14.11	
	0.370	46.97	
	1.100	73.12	
	3.300	86.71	
	10.000	96.13	
	30.000	97.01	30.400
217	0.123	<10	
	0.370	<10	
	1.100	<10	
	3.300	33.1	
	10.000	62.4	
	30.000	69.08	
218	0.123	<10	
	0.370	<10	
	1.100	21.21	
	3.300	45.95	
	10.000	59.29	

-252-

Example No.	HIV Protease FITC Assay		
	HIV-1 Dose (uM)	HIV-1 Protease % Inhib	HIV-1 FITC Ki (nM)
	30.000	58.22	
228	0.123	<10	
	0.370	63.94	
	1.100	93.39	
5	3.300	106.45	
	10.000	112.12	
	30.000	104.72	17.400
240	0.123	<10	
	0.370	40.59	
10	1.100	68.74	
	3.300	95.05	
	10.000	113.15	
	30.000	104.47	29.200
241	0.123	<10	
15	0.370	<10	
	1.100	32.77	
	3.300	62.87	
	10.000	87.09	
	30.000	90.26	
20	242	0.123	<10
	0.370	19.85	
	1.100	53.5	
	3.300	80.54	
	10.000	90.2	
25		30.000	93.21
	219	0.123	<10
	0.370	<10	
	1.100	35.32	
	3.300	65.61	
30	10.000	79.7	

-253-

Example No.	HIV Protease FITC Assay		
	HIV-1 Dose (uM)	HIV-1 Protease % Inhib	HIV-1 FITC Ki (nM)
	30.000	90.2	
220	0.123	<10	
	0.370	<10	
	1.100	21.33	
5	3.300	51.63	
	10.000	68.42	
	30.000	62.18	
229	0.123	52.16	
	0.370	95.94	
10	1.100	106.04	
	3.300	105.97	
	10.000	113.33	
	30.000	101.62	3.500
230	0.123	<10	
15	0.370	15.32	
	1.100	48.57	
	3.300	71.34	
	10.000	91.07	
	30.000	85.27	
20	231	0.123	16.51
	0.370	57.42	
	1.100	77.7	
	3.300	98.89	
	10.000	112.59	
25		30.000	109.07
	209	0.123	<10
	0.370	11.99	
	1.100	32.18	
	3.300	59.85	
30		10.000	76.68

-254-

Example No.	HIV Protease FITC Assay		
	HIV-1 Dose (uM)	HIV-1 Protease % Inhib	HIV-1 FITC Ki (nM)
	30.000	77.84	92.000
210	0.123	<10	
	0.370	<10	
	1.100	37.5	
5	3.300	61.03	
	10.000	74.98	
	30.000	86.03	78.000
211	0.123	<10	
	0.370	21.39	
10	1.100	47.29	
	3.300	66.35	
	10.000	89.15	
	30.000	92.11	64.000
248	0.123	<10	
15	0.370	31.61	
	1.100	63.69	
	3.300	86.48	
	10.000	101.36	
	30.000	99.16	61.700
20	249	0.123	<10
	0.370	39.95	
	1.100	70.35	
	3.300	88.52	
	10.000	103.18	
25		30.000	107
			44.400
250			-15.000

TABLE III

EXAMPLE NO.	ACTUAL
80	368.2354
81	364.2025
82	310.1562
83	274.1572
84	328.2038
85	380.2350
86	374.1877
87	352.2044
88	400.2045
89	310.1564
90	338.1884
91	374.1876
92	370.2504
93	402.2189
94	366.2195
95	394.2508
96	298.1567
97	336.1724
98	296.1410
99	388.2028
100	376.0675
101	424.2025
102	358.1778
103	460.2479
104	284.1420
105	412.0669
106	386.2100
107	448.2259
108	402.2044
109	350.0518

5

EXAMPLE NO.	ACTUAL
110	414.2400
111	440.0986
112	510.2982
113	356.1614
114	358.1786
115	314.1524
116	316.1676

-257-

TABLE IV

MEAN ABSOLUTE AND RELATIVE (%) PROSTATE WEIGHTS IN MALE DOGS

	Group No.	Dose (mg/kg/day)	Relative Weight*	Absolute Weight (Gms)
5	1	0	0.096	9.55
	2	50	0.088	8.87
	3	100	0.074	7.55
	4	200	0.046	4.58
	5	400	0.044	4.43
10	6	0	0.076	7.98
	7	400	0.055	5.65

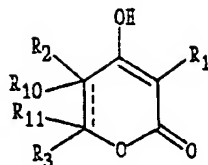
*% body weight

15

-258-

CLAIMS

1. A compound of the formula I



I

wherein R_1 is

- a) $-(CH_2)_n-CH(R_5)-(CH_2)_m-R_4$,
 b) $-CH(aryl)-CH[C(O)-O-C_1-C_6 \text{ alkyl}]_2$,
 c) $-C(C_3-C_5 \text{ cycloalkyl})-(CH_2)_n-R_4$,
 d) $-C(aryl)=CH-aryl$, or
 e) $-CH(R_5)-S-(CH_2)_m-R_4$;

wherein R_2 is

- a) hydrogen,
 b) halo,
 c) $C_1-C_6 \text{ alkyl}-[O-(CH_2)_2]_q-(CH_2)_n$, or
 d) $C_1-C_6 \text{ alkyl}$;

wherein R_3 is

- a) $C_2-C_{10} \text{ alkyl}$ optionally substituted by zero (0) to five (5) halo,
 b) $C_2-C_{10} \text{ alkenyl}$,
 c) $R_4-(CH_2)_m-CH(R_6)-(CH_2)_n$,
 d) $R_4-(CH_2)_p$,
 e) $R_4-CH=CH$,
 f) $CH_2=CH-(CH_2)_p$,
 g) $R_4(CH_2)_mX_1C(O)(CH_2)_n$,
 h) $R_4(CH_2)_mC(O)X_1(CH_2)_n$,
 i) aryl,
 j) het,
 k) $C_3-C_7 \text{ cycloalkyl}$,
 l) $C_1-C_6 \text{ alkyl}-O-C(O)-(CH_2)_n$,
 m) $C_1-C_6 \text{ alkyl}-[O-(CH_2)_2]_q-(CH_2)_n$,
 n) $R_4-CH(R_6)-CH(R_6)$,
 p) $R_{12}-(CH_2)_m-X_2-(CH_2)_n-(R_7)HC$, or
 q) $R_{15}-(CH_2)_m-X_2-(CH_2)_n-(R_7)HC$;

wherein R_4 is

- a) aryl,
- b) het,
- c) C_3 - C_7 cycloalkyl,
- 5 d) C_2 - C_{10} alkenyl,
- e) C_1 - C_6 alkyl-[O-(CH_2)₂]_q-(CH_2)_n,
- f) halo,
- g) het-O-,
- h) het-C(O)-,
- 10 i) aryl-(CH_2)_n-O-C(O)-, or
- j) trifluoromethyl;

wherein R_5 is

- a) C_1 - C_{10} alkyl,
- b) C_2 - C_{10} alkenyl,
- 15 c) C_3 - C_7 cycloalkyl,
- d) -(CH_2)_n-aryl,
- e) -(CH_2)_p-het, or
- f) -(CH_2)_n-CH=CH-aryl;

wherein R_6 is

- 20 a) C_1 - C_{10} alkyl,
- b) R_4 - C_1 - C_5 alkyl,
- c) -(CH_2)_n- C_3 - C_7 cycloalkyl,
- d) -(CH_2)_p-CH=CH₂,
- e) -(CH_2)_p-aryl,
- 25 f) -(CH_2)_p-het, or
- g) hydroxy-;

wherein X_1 is -NR₇-;

wherein R_7 is

- a) hydrogen, or
- 30 b) C_1 - C_5 alkyl;

wherein aryl is

- a) phenyl substituted by zero (0) to three(3) R_8 ,
- b) naphthyl substituted by zero (0) to three(3) R_8 ,
- c) biphenyl substituted by zero (0) to three (3) R_8 , or
- 35 d) perhalophenyl;

wherein het is a 5- or 6-membered saturated or unsaturated ring containing from one (1) to four

(4) heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring, C₃-C₈ cycloalkyl, or another heterocycle; and if chemically feasible, the nitrogen and sulfur atoms may be in the oxidized forms; and substituted by zero (0) to three (3) R₉;

5 wherein R₈ and R₉ are independently

- a) C₁-C₈ alkyl substituted by zero (0) to three (3) halo,
- b) C₂-C₈ alkenyl,
- c) hydroxy,
- d) hydroxy-C₁-C₅ alkyl,
- 10 e) -(CH₂)_n-O-C₁-C₅ alkyl substituted by zero (0) to three (3) hydroxy,
- f) -(CH₂)_n-O-C₂-C₇ alkenyl substituted by zero (0) to three (3) hydroxy,
- g) halo,
- h) amino,
- i) amino-C₁-C₅ alkyl,
- 15 j) mono-or di-C₁-C₅ alkylamino,
- k) -C(O)-C₁-C₅ alkyl,
- l) -CHO,
- m) -COOH,
- n) -COOC₁-C₅alkyl,
- 20 o) -CON(R₇)₂,
- p) C₃-C₇ cycloalkyl,
- q) nitro,
- r) -CN,
- s) -SO₃H,
- 25 t) -SO₂NH₂,
- u) -O[(CH₂)₂-O]_q-CH₃,
- v) -[CH₂-O]_q-C₁-C₃ alkyl,
- w) -(CH₂)_n-NHC(O)-O-(CH₂)_p-R₁₂,
- x) -(CH₂)_n-NHC(O)-O-(CH₂)_p-R₁₅,
- 30 y) -(CH₂)_n-R₁₂,
- z) -SO₂-R₁₂,
- a1) -(CH₂)_n-X₂-(CH₂)_n-R₁₂,
- b1) -(CH₂)_n-X₂-(CH₂)_n-R₁₅,
- c1) -(CH₂)_n-X₂-CH=CH-R₁₂,
- 35 d1) -(CH₂)_n-X₂-CH=CH-R₁₅,
- e1) -(CH₂)_n-X₂-C₁-C₁₀alkyl substituted by zero (0) to three (3) halo,

- f1) $-(CH_2)_n-X_2-C_2-C_5$ alkenyl,
 g1) $-X_2-(CH_2)_p-CH(NH_2)(COOH)$,
 h1) $-NHCONH-SO_2-R_{12}$,
 i1) $-X_2-(CH_2)_p-NH-C(O)-O-C_1-C_6$ alkyl,
 5 j1) $-X_2-CH(X_3)-NH-C(O)-O-C_1-C_6$ alkyl,
 k1) $-X_2-(CH_2)_p-CH[NH-C(O)-O-(CH_2)_p-R_{12}]-C(O)-O-(CH_2)_p-R_{12}$,
 l1) $-(CH_2)_n-X_4-N(C_1-C_3 \text{ alkyl})_2$,
 m1) $-(CH_2)_n-X_4-NHR_{12}$,
 n1) $-NH-AA-P_1$,
 10 o1) $-(CH_2)_p-N_3$,
 p1) $-(CH_2)_p-R_{12}$,
 q1) $-(CH_2)_p-R_{15}$,
 r1) $-(CH_2)_n-NHC(SCH_3)=CHNO_2$,
 s1) $-(CH_2)_n-NHC(NHR_7)=CHNO_2$,
 15 t1) $-(CH_2)_n-NHC(SCH_3)=NCN$, or
 u1) $-(CH_2)_n-NHC(NHR_7)=NCN$;

wherein X_2 is

- a) $-NH-C(O)-$,
 b) $-NH-SO_2-$,
 20 c) $-NH-C(O)-NH-$, or
 d) $-SO_2-NH-$;

wherein X_3 is

- a) C_1-C_6 alkyl, or
 b) $-(CH_2)_p-R_{15}$;

25 wherein X_4 is

- a) $-NH-C(O)-$, or
 b) $-NH-SO_2-$;

wherein R_{10} is hydrogen;

wherein R_{11} is

- 30 a) hydrogen,
 b) C_1-C_6 alkyl,
 c) $-(CH_2)_n$ -aryl,
 d) $-(CH_2)_n-C_3-C_7$ cycloalkyl, or
 e) $-(CH_2)_n$ -het;

35 or wherein R_{10} and R_{11} taken together form a double bond;
 or wherein R_3 and R_{11} taken together form

-262-

a) C_3-C_8 cycloalkyl substituted by zero (0) to three (3) hydroxy, $=N-OH$, $=O$ (oxo), or protected form thereof, or substituted at the α -position by R_{14} ; or

b) a 5- or 6-membered saturated ring containing one (1) or two (2) oxygen atoms;

wherein R_{12} is

5 a) phenyl substituted by zero (0) to three (3) R_{13} , or

b) naphthyl substituted by zero (0) to three (3) R_{13} ;

wherein R_{13} is

a) C_1-C_{10} alkyl substituted by zero (0) to three (3) halo,

b) hydroxy,

10 c) hydroxy- C_1-C_5 alkyl,

d) $-(CH_2)_n-O-C_1-C_5$ alkyl substituted by zero (0) to three (3) hydroxy or halo,

e) $-(CH_2)_n-O-C_2-C_7$ alkenyl substituted by zero (0) to three (3) hydroxy or halo,

f) halo,

g) amino,

15 h) amino C_1-C_5 alkyl,

i) mono- or di- C_1-C_5 alkylamino,

j) $-C(O)-C_1-C_5$ alkyl,

k) $-CHO$,

l) $-COOH$,

20 m) $-CON(R_7)_2$,

n) $-NHCOC_1-C_3$ alkyl,

o) $-NHOH$,

p) nitro,

q) $-CN$,

25 r) $-(CH_2)_n$ -phenyl,

s) $-COOC_1-C_5$ alkyl, or

t) $-SO_2$ -phenyl substituted by zero (0) to three (3) C_1-C_5 alkyl,

u) $-(CH_2)_n-X_4$ -phenyl, or

v) $-(CH_2)_n-N=N$ -phenyl substituted by zero (0) or one (1) $-N(C_1-C_3 \text{ alkyl})_2$;

30 wherein R_{14} is

a) $-(CH_2)_n$ -aryl,

b) $-C_1-C_6$ alkyl, or

c) $-(CH_2)_n-C_4-C_7$ cycloalkyl;

wherein R_{15} is a 5- or 6-membered saturated or unsaturated ring containing from one (1) to four

35 (4) heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring. C_3 -

C₃ cycloalkyl, or another heterocycle; and substituted by zero (0) to three (3) R₁₃;

wherein AA is an amino acid residue;

wherein P₁ is hydrogen or a nitrogen protecting group;

wherein m and n are independently zero (0) to five (5) inclusive;

5 wherein p is one (1) to five (5) inclusive;

wherein q is one (1) to five (5) inclusive; and

pharmaceutically acceptable salts thereof.

2. The compound of claim 1 provided that when R₁ is -(CH₂)_n-CH(R₅)-(CH₂)_m-R₄, -
 10 C(C₃-C₅cycloalkyl)-(CH₂)_n-R₄, or -CH(R₅)-S-(CH₂)_m-R₄, R₄ is aryl, het or C₃-C₇ cycloalkyl.

3. The compound of claim 1

wherein R₁ is -CH(R₅)-R₄;

wherein R₂ is hydrogen;

15 wherein R₃ is

a) C₃-C₈ alkyl,

b) R₄-(CH₂)_m-CH(R₆)-,

c) R₄-(CH₂)_p-,

d) R₄-CH=CH-,

20 e) CH₂=CH-(CH₂)_p-,

f) R₄-NH-C(O)-CH₂-,

wherein R₄ is aryl;

wherein R₅ is

a) C₂-C₅ alkyl,

25 b) C₂-C₅ alkenyl,

c) cyclopropyl;

wherein R₆ is

a) C₂-C₅ alkyl, or

b) R₄-C₁-C₂ alkyl-;

30 wherein aryl is

a) phenyl substituted by zero (0) to three (3) R₈, or

b) naphthyl substituted by zero (0) to three (3) R₈;

wherein R₈ is

a) halo, or

35 b) C₁-C₃ alkoxy;

wherein R₁₀ and R₁₁ taken together form a double bond;

-264-

wherein m is one (1) to three (3) inclusive;

wherein p is one (1) to three (3) inclusive.

4. The compound of claim 3

5 wherein R_1 is $-\text{CH}(R_5)-R_4$;

wherein R_2 is hydrogen;

wherein R_3 is

- a) $\text{C}_5\text{-C}_8$ alkyl,
- b) $R_4-(\text{CH}_2)_m-\text{CH}(R_6)-$,
- 10 c) $R_4-(\text{CH}_2)_p-$,
- d) $\text{CH}_2=\text{CH}-(\text{CH}_2)_p-$, or
- e) $R_4-\text{CH}=\text{CH}-$;

wherein R_4 is aryl;

wherein R_5 is

- 15 a) ethyl,
- b) ethenyl, or
- c) cyclopropyl;

wherein R_6 is

- a) ethyl, or
- 20 b) $R_4-\text{CH}_2-$;

wherein aryl is

- a) phenyl substituted by zero (0) to three (3) R_8 , or
- b) naphthyl substituted by zero (0) to three (3) R_8 ;

wherein R_8 is

- 25 a) halo, or
- b) methoxy;

wherein R_{10} and R_{11} taken together form a double bond;

wherein m is one or two;

wherein p is two (2) or three (3).

30

5. The compound of claim 3 selected from the group consisting of:

- 3-(α -ethylbenzyl)-4-hydroxy-6-phenyl-2H-Pyran-2-one;
- 6-benzyl-3-(α -ethylbenzyl)-4-hydroxy-2H-Pyran-2-one;
- 3-(α -ethylbenzyl)-6-phenethyl-4-hydroxy-2H-Pyran-2-one;
- 35 4-hydroxy-6-phenethyl-3-(α -propyl-p-bromobenzyl)-2H-Pyran-2-one;
- 6-(p-bromophenethyl)-3-(α -ethylbenzyl)-4-hydroxy-2H-Pyran-2-one;

-265-

- 3-(.alpha.-ethylbenzyl)-6-(o-fluorophenethyl)-4-hydroxy-2H-Pyran-2-one;
 3-(.alpha.-ethylbenzyl)-4-hydroxy-6-(3-phenylpropyl)-2H-Pyran-2-one;
 3-(.alpha.-ethylbenzyl)-4-hydroxy-6-propyl-2H-Pyran-2-one;
 3-(.alpha.-ethylbenzyl)-4-hydroxy-6-(3-butenyl)-2H-Pyran-2-one;
 5 3-(.alpha.-ethylbenzyl)-4-hydroxy-6-[(phenylamino)carbonyl]methyl]-2H-Pyran-2-one;
 4-hydroxy-6-phenethyl-3-(.alpha.-vinylbenzyl)-2H-Pyran-2-one;
 3-(.alpha.-ethylbenzyl)-6-(.alpha.-ethylphenethyl)-4-hydroxy-2H-Pyran-2-one;
 3-([R]-.alpha.-ethylbenzyl)-4-hydroxy-6-([R]-.alpha.-ethylphenethyl)-2H-pyran-2-one;
 3-([R]-.alpha.-ethylbenzyl)-4-hydroxy-6-([S]-.alpha.-ethylphenethyl)-2H-pyran-2-one;
 10 3-([S]-.alpha.-ethylbenzyl)-4-hydroxy-6-([R]-.alpha.-ethylphenethyl)-2H-pyran-2-one;
 3-([S]-.alpha.-ethylbenzyl)-4-hydroxy-6-([S]-.alpha.-ethylphenethyl)-2H-pyran-2-one;
 Sodium (3S,6R) 3-(.alpha.-ethylbenzyl)-6-(.alpha.-ethylphenethyl)-2H-pyran-2-one 4-oxide;
 3-(.alpha.-ethylbenzyl)-1-ethylpropyl-4-hydroxy-2H-Pyran-2-one;
 3-(.alpha.-ethylbenzyl)-4-hydroxy-6-(p-methoxystyryl)-2H-Pyran-2-one;
 15 3-(.alpha.-ethylbenzyl)-4-hydroxy-6-(2-naphth-2-ylethyl)-2H-Pyran-2-one;
 3-(.alpha.-ethylbenzyl)-4-hydroxy-6-(1-ethyl-2-naphth-2-ylethyl)-2H-Pyran-2-one;
 3-(.alpha.-ethylbenzyl)-4-hydroxy-6-(2-naphth-1-ylethyl)-2H-Pyran-2-one;
 3-(.alpha.-ethylbenzyl)-4-hydroxy-6-(1-ethyl-2-naphth-1-ylethyl)-2H-Pyran-2-one;
 3-(.alpha.-cyclopropylbenzyl)-4-hydroxy-6-(3-phenylpropyl)-2H-Pyran-2-one;
 20 3-(.alpha.-cyclopropylbenzyl)-6-(1-ethyl propyl)-4-hydroxy-2H-Pyran-2-one;
 3-(.alpha.-cyclopropylbenzyl)-6-(.alpha.-benzylphenethyl)-4-hydroxy-2H-Pyran-2-one;
 3-(.alpha.-cyclopropylbenzyl)-4-hydroxy-6-phenethyl-2H-Pyran-2-one; and
 3-(.alpha.-cyclopropylbenzyl)-6-(1-propylbutyl)-4-hydroxy-2H-Pyran-2-one.

- 25 6. The compound selected from the group consisting of:
 3-(.alpha.-cyclopropylbenzyl)-4-hydroxy-6-methyl-2H-Pyran-2-one; and
 4-Hydroxy-6-methyl-3-(3-phenyl-prop-2-enyl)-2H-pyran-2-one.

7. The compound of claim 1
 30 wherein R_1 is

- a) $-(CH_2)_n-CH(R_2)-(CH_2)_m-R_4$,
 b) $-CH(aryl)-CH[C(O)-O-C_1-C_6 \text{ alkyl}]_2$, or
 c) $-C(aryl)=CH-aryl$;

wherein R_2 is hydrogen;

- 35 wherein R_3 is

- a) C_2-C_4 alkyl,

- b) $R_4-(CH_2)_p-$,
- c) aryl, or
- d) cyclohexyl;

wherein R_4 is

- 5 a) aryl, or
- b) het;

wherein R_5 is

- a) ethyl,
- b) ethenyl,
- 10 c) cyclopropyl,
- d) $-(CH_2)_n$ -aryl, or
- e) $-(CH_2)_n-CH=CH$ -aryl;

wherein R_{10} is hydrogen;

wherein R_{11} is

- 15 a) hydrogen,
- b) C_1 - C_4 alkyl,
- c) $-(CH_2)_n$ -aryl, or
- d) cyclohexyl;

or wherein R_3 and R_{11} taken together form

- 20 a) C_3 - C_8 cycloalkyl substituted by zero (0) to three (3) hydroxy, =N-OH, carbonyl group, or protected form thereof, or substituted at the α -position by $-(CH_2)_n$ -aryl, or
- b) a 5- or 6-membered saturated ring containing one (1) or two (2) oxygen atoms;

wherein aryl is phenyl substituted by zero (0) to three (3) R_8 ;

wherein het is

- 25 a) thiophenyl substituted by zero (0) to three (3) R_9 , or
- b) furanyl substituted by zero (0) to three (3) R_9 ;

wherein R_8 and R_9 are independently

- a) nitro,
- b) hydroxy,
- 30 c) methyl, or
- d) $-(CH_2-O)_q-C_1-C_3$ alkyl;

wherein m is zero (0);

wherein n is zero (0) to three (3), inclusive;

wherein p is one (1) to three (3), inclusive;

- 35 wherein q is two (2).

8. The compound of claim 7 selected from the group consisting of:
 Dimethyl 3-[(4-hydroxy-2-oxo-6-phenyl-2H-1-pyran-3-yl)(4-nitrophenyl)-1,3-propandioate;
 Dimethyl 3-[(4-hydroxy-2-oxo-6-phenyl-2H-1-pyran-3-yl)(3-nitrophenyl)-1,3-propandioate;
 5 6-Ethyl-3-(α -ethylbenzyl)-6-phenyl-tetrahydropyran-2,4-dione;
 5,6-Dihydro-4-hydroxy-6-cyclohexyl-6-phenyl-3-[1-(3-hydroxyphenyl)propyl]-2H-pyran-2-one;
 4-Hydroxy-1-oxa-3-(1-phenylpropyl)spiro[5.5]undec-3-en-2-one, sodium salt;
 10 6,6-Diethyl-3-(3-phenylpropyl)-tetrahydropyran-2,4-dione;
 Dihydro-6-methyl-6-phenyl-3-(1-phenyl-2-propenyl)-2H-Pyran-2,4(3H)-dione;
 Dihydro-3-(1-(3-hydroxyphenyl)propyl)-6-phenyl-6-propyl-2H-pyran-2,4(3H)-dione;
 5,6-Dihydro-4-hydroxy-6-phenyl-6-propyl-3-(1-phenylpropyl)-2H-pyran-2-one;
 5,6-Dihydro-4-hydroxy-6-phenyl-6-propyl-3-[1-(3-hydroxyphenyl)propyl]-2H-pyran-2-one;
 15 one;
 12-Hydroxy-11-(1-phenyl-allyl)-1,4,9-trioxa-dispiro[4.2.5.2]pentadec-11-en-10-one;
 12-Hydroxy-11-(1-phenyl-propyl)-1,4,9-trioxa-dispiro[4.2.5.2]pentadec-11-en-10-one;
 4-Hydroxy-3-(1-phenyl-propyl)-1-oxa-spiro[5.5]undec-3-ene-2,9-dione;
 6,6-Dibenzyl-4-hydroxy-3-(1-phenyl-propyl)-5,6-dihydro-pyran-2-one;
 20 4-Hydroxy-3-(1-phenyl-allyl)-1,9-dioxa-spiro[5.5]undec-3-en-2-one;
 4,9-Dihydroxy-3-(1-phenyl-propyl)-1-oxa-spiro[5.5]undec-3-en-2-one;
 5,6-Dihydro-4-hydroxy-6-phenyl-6-(phenylmethyl)-3-(1-phenyl-2-propenyl)-2H-pyran-2-one;
 5,6-Dihydro-4-hydroxy-6-phenyl-6-(phenylmethyl)-3-(1-phenylpropyl)-2H-pyran-2-one;
 25 3-(1,3-Diphenyl-2-propenyl)-5,6-dihydro-4-hydroxy-6-(2-phenylethyl)-6-propyl-, (E)-2H-pyran-2-one;
 3-(1,3-Diphenyl-2-propyl)-5,6-dihydro-4-hydroxy-6-(2-phenylethyl)-6-propyl-, (E)-2H-pyran-2-one;
 3-(1,3-Diphenyl-2-propenyl)-5,6-dihydro-4-hydroxy-6-phenyl-6-(phenylmethyl)-2H-pyran-2-one;
 30 3-(1,2-Diphenylethenyl)-5,6-dihydro-4-hydroxy-6-(2-phenylethyl)-6-propyl-, (E)-2H-pyran-2-one;
 5,6-Dihydro-4-hydroxy-6-(2-phenylethyl)-3-(1-phenyl-2-propenyl)-6-propyl-2H-pyran-2-one;
 one;
 35 5,6-Dihydro-4-hydroxy-6-(2-phenylethyl)-3-(1-phenylpropyl)-6-propyl-2H-pyran-2-one;
 3-(1,3-Diphenyl-2-propenyl)-5,6-dihydro-4-hydroxy-6-(phenylmethyl)-6-propyl-2H-

- pyran-2-one;
 3-(1,3-Diphenylpropyl)-5,6-dihydro-4-hydroxy-6-(phenylmethyl)-6-propyl-2H-pyran-2-one;
 one;
 4-Hydroxy-3-(1-phenylallyl)-1-oxa-spiro[5.6]-dodec-3-en-2-one;
 5 4-Hydroxy-3-(1-phenylallyl)-1-oxa-spiro[5.4]-dec-3-en-2-one;
 7-Benzyl-4-hydroxy-3-(1-phenylallyl)-1-oxa-spiro[5.5]undec-3-en-2-one;
 4-Hydroxy-3-(1-phenylpropyl)-1-oxa-spiro[5.4]-dec-3-en-2-one;
 4-Hydroxy-3-(1-phenyl-2-propenyl)-1-oxaspiro[5.7]tridec-3-en-2-one;
 4-Hydroxy-3-(1-phenylpropyl)-1-oxaspiro[5.7]tridec-3-en-2-one;
 10 6-Butyl-5,6-dihydro-3-(1,3-diphenyl-2-propenyl)-4-hydroxy-6-phenylmethyl-2H-pyran-2-one;
 one;
 6-Butyl-5,6-dihydro-3-(1,3-diphenylpropyl)-4-hydroxy-6-phenylmethyl-2H-pyran-2-one;
 6-Butyl-5,6-dihydro-4-hydroxy-6-phenylmethyl-3-(1-phenyl-2-propenyl)-2H-pyran-2-one;
 6-Butyl-5,6-dihydro-4-hydroxy-6-phenylmethyl-3-(1-phenylpropyl)-2H-pyran-2-one;
 15 3-(α -Cyclopropyl-[5-(methoxymethoxy-methyl)-thiophen-2-yl]-methyl)-5,6-dihydro-4-hydroxy-6-(2-methylpropyl)-6-(2-phenylethyl)-2H-pyran-2-one;
 5,6-Dihydro-4-hydroxy-6-(2-methylpropyl)-6-(2-phenylethyl)-3-(1-phenyl-2-propenyl)-2H-pyran-2-one;
 5,6-dihydro-4-hydroxy-6-(2-methylpropyl)-6-(2-phenylethyl)-3-(1-phenylpropyl)-2H-pyran-2-one;
 20 5,6-Dihydro-3-diphenylmethyl-4-hydroxy-6,6-di-(2-phenylethyl)-2H-pyran-2-one;
 5,6-Dihydro-4-hydroxy-6,6-di-(2-phenylethyl)-3-(1,3-diphenyl-2-propenyl)-2H-pyran-2-one;
 one;
 5,6-Dihydro-4-hydroxy-6,6-di-(2-phenylethyl)-3-(1,3-diphenylpropyl)-2H-pyran-2-one;
 25 5,6-Dihydro-4-hydroxy-3-(1,3-diphenyl-2-propenyl)-6-(3-phenylpropyl)-6-propyl-2H-pyran-2-one;
 5,6-Dihydro-4-hydroxy-3-(1,3-diphenylpropyl)-6-(3-phenylpropyl)-6-propyl-2H-pyran-2-one;
 one;
 3-(α -Cyclopropyl-[5-(methoxymethoxy-methyl)-thiophen-2-yl]-methyl)-5,6-dihydro-4-hydroxy-6-(2-phenylethyl)-6-propyl-2H-pyran-2-one;
 30 3-(α -Cyclopropyl-[5-(methoxymethoxy-methyl)-thiophen-2-yl]-methyl)-5,6-dihydro-4-hydroxy-6-(3-phenylpropyl)-6-propyl-2H-pyran-2-one;
 5,6-Dihydro-3-diphenylmethyl-4-hydroxy-6-(3-phenylpropyl)-6-propyl-2H-pyran-2-one;
 3-Diphenylmethyl-5,6-dihydro-4-hydroxy-6-(2-methylpropyl)-6-(2-phenylethyl)-2H-pyran-2-one;
 35 3-(1,3-Diphenyl-2-propenyl)-5,6-dihydro-4-hydroxy-6-(2-methylpropyl)-6-(2-

phenylethyl)-2H-pyran-2-one; and

3-(1,3-Diphenyl-2-propyl)-5,6-dihydro-4-hydroxy-6-(2-methylpropyl)-6-(2-phenylethyl)-2H-pyran-2-one.

5 9. The compound of claim 1

wherein R_1 is

- a) $-(CH_2)_n-CH(R_5)-(CH_2)_m-R_4$, or
- b) $-C(C_3-C_5\text{cycloalkyl})-(CH_2)_n-R_4$;

wherein R_2 is

- 10 a) hydrogen, or
- b) halo;

wherein R_3 is

- a) $R_4-(CH_2)_m-CH(R_6)-(CH_2)_n$,
- b) $R_4-(CH_2)_p$,
- 15 c) C_3-C_6 alkyl substituted by zero (0) to three (3) halo, or
- d) $R_4-CH(R_6)-CH(R_6)$;

wherein R_4 is

- a) aryl,
- b) het,
- 20 c) C_3-C_5 cycloalkyl,
- d) $CH_2=CH-$
- e) $CH_3-[O-(CH_2)_2]_q-$
- f) halo,
- g) het-O-, or
- 25 h) aryl- $(CH_2)_n-O-C(O)-$;

wherein R_5 is

- a) ethyl,
- b) cyclopropyl, or
- c) $-CH_2$ -aryl;

30 wherein R_6 is

- a) ethyl,
- b) propyl,
- c) $-CH_2$ -cyclopropyl,
- d) $-CH_2-CH=CH_2$,
- 35 e) $-CH_2$ -aryl, or
- f) hydroxy;

-270-

wherein aryl is phenyl substituted by zero (0) to three (3) R_8 ;

wherein het substituted by zero (0) to three (3) R_9 is

- a) indolyl,
- b) tetrahydro-furanyl,
- 5 c) thiophenyl,
- d) isoxazolyl,
- e) tetrahydro-furanyl,
- f) tetrahydro-pyranyl,
- g) furanyl,
- 10 h) (1,3)dioxolanyl,
- i) pyridinyl,
- j) morpholinyl,
- k) piperidinyl,
- l) pyrrolidinyl, or
- 15 m) pyrrolidinonyl.

wherein R_8 is

- a) $-X_2-(CH_2)_p-NH-C(O)-O-C_1-C_6$ alkyl,
- b) $-(CH_2)_n-X_2-(CH_2)_n-R_{12}$,
- c) $-(CH_2)_n-X_2-(CH_2)_n-R_{15}$,
- 20 d) $-(CH_2)_n-NHC(O)-O-(CH_2)_p-R_{12}$,
- e) $-NH-C(O)-NH-SO_2-R_{12}$,
- f) $-X_2-CH(X_3)-NHC(O)-O-C_1-C_6$ alkyl,
- g) $-X_2-(CH_2)_p-CH[NH-C(O)-O-(CH_2)_p-R_{12}]-C(O)-O-(CH_2)_p-R_{12}$,
- h) $-X_2-(CH_2)_p-CH(NH_2)(COOH)$,
- 25 i) C_1-C_5 alkyl substituted by zero (0) to three (3) halo,
- j) halo, or
- k) C_1-C_5 alkyloxy;

wherein R_9 is

- a) methyl,
- 30 b) halo,
- c) $-(CH_2)_n-R_{12}$,
- d) $-SO_2-R_{12}$,

wherein X_2 is

- a) $-NH-C(O)-$, or
- 35 b) $-NH-C(O)-NH-$;

wherein X_3 is

-271-

a) C_1-C_6 alkyl, orb) $-(CH_2)_p-R_{15}$;wherein R_{10} and R_{11} taken together form a double bond;wherein R_{12} is phenyl substituted by zero (0) to three (3) R_{13} ;5 wherein R_{13} is

a) methoxy,

b) halo,

c) $-SO_2$ -phenyl substituted by zero (0) or one (1) C_1-C_5 alkyl,d) $-CN$, or10 e) C_1-C_5 alkyl;wherein R_{15} substituted by zero (0) or one (1) R_{13} is

a) indolyl,

b) pyridyl,

c) imidazolyl, or

15 d) quinoliny;

wherein m is zero (0) to three (3), inclusive;wherein n is zero (0) to two (2), inclusive;wherein p is one (1) to three (3), inclusive;wherein q is two (2) or three (3).

20

10. The compound of claim 9 provided that when R_1 is $-(CH_2)_n-CH(R_5)-(CH_2)_m-R_4$ or $-C(C_3-C_5\text{cycloalkyl})-(CH_2)_n-R_4$, R_4 is aryl, het or C_3-C_5 cycloalkyl.

11. The compound of claim 10 selected from the group consisting of:

25 N-(3-Cyclopropyl-[6-(1-ethyl-phenethyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl)-phenyl)-3-(*tert*-butyloxycarbonylamino)-propionamide;

N-(3-{Cyclopropyl-[6-(2-cyclopropyl-1-cyclopropylmethyl-ethyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-3-indol-1-yl-propionamide;

30 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(1-(tetrahydro-furan-3-ylmethyl)-propyl)-pyran-2-one;

6-(1-(5-Chloro-thiophen-2-ylmethyl)-propyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one;

3-(Cyclopropyl-phenyl-methyl)-6-(1-(3,5-dimethyl-isoxazol-4-ylmethyl)-propyl)-4-hydroxy-pyran-2-one;

35 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(1-(tetrahydro-furan-2-ylmethyl)-propyl)-pyran-2-one;

- 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(1-thiophen-2-ylmethyl-propyl)-pyran-2-one;
3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(1-tetrahydro-pyran-4-ylmethyl)-propyl)-
pyran-2-one;
3-(Cyclopropyl-phenyl-methyl)-6-(1-furan-2-ylmethyl-propyl)-4-hydroxy-pyran-2-one;
5 3-(Cyclopropyl-phenyl-methyl)-6-(1-(1,3)dioxolan-2-ylmethyl-propyl)-4-hydroxy-pyran-
2-one;
3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(1-(tetrahydro-pyran-3-ylmethyl)-propyl)-
pyran-2-one;
3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(1-(tetrahydro-pyran-2-ylmethyl)-propyl)-
10 pyran-2-one;
3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(1-pyridin-2-ylmethyl-propyl)-pyran-2-one;
6-(4-Chloro-1-ethyl-butyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one;
6-(3-Chloro-1-ethyl-propyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one;
3-(Cyclopropyl-phenyl-methyl)-6-[ethyl-3-(tetrahydro-pyran-2-yloxy)-propyl]-4-hydroxy-
15 pyran-2-one;
3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(1-pyridin-3-ylmethyl-propyl)-pyran-2-one;
3-(Cyclopropyl-phenyl-methyl)-6-(1-ethyl-3-thiophen-3-yl-propyl)-4-hydroxy-pyran-2-
one;
3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-[1-(tetrahydro-pyran-3-ylmethyl)-butyl]-
20 pyran-2-one;
5-Bromo-6-(2-cyclopropyl-cyclopropylmethyl-ethyl)-4-hydroxy-3-(1-phenyl-propyl)-
pyran-2-one;
3-(1-Benzyl-2-phenyl-ethyl)-6-(2-cyclopropyl-1-cyclopropylmethyl-ethyl)-4-hydroxy-
pyran-2-one;
25 6-(2-Cyclopropylmethyl-ethyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one;
6-(1-Allyl-but-3-enyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one;
3-(Cyclopropyl-phenyl-methyl)-6-(1-ethyl-3-(2-methoxy-ethoxy)-propyl)-4-hydroxy-
pyran-2-one;
6-(1-Benzyl-3-(2-methoxy-ethoxy)-propyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-
30 pyran-2-one;
3-(α -cyclopropylbenzyl)-4-hydroxy-6-(α -ethyl- β -hydroxyphenethyl)-2H-pyran-2-one;
3-(α -cyclopropylbenzyl)-4-hydroxy-6-(β -hydroxy-p-methylphenethyl)-2H-pyran-2-one;
3-(α -cyclopropylbenzyl)-4-hydroxy-6-(β -hydroxy-p-fluorophenethyl)-2H-pyran-2-one;
3-(α -cyclopropylbenzyl)-4-hydroxy-6-(β -hydroxy-p-chlorophenethyl)-2H-pyran-2-one;
35 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(β -hydroxy-m-chlorophenethyl)-2H-pyran-2-one;
3-(α -cyclopropylbenzyl)-4-hydroxy-6-(β -hydroxy-o-chlorophenethyl)-2H-pyran-2-one;

- 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(2-(furan-3-yl)-2-hydroxyethyl)-2H-pyran-2-one;
 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(2-(thiophen-3-yl)-2-hydroxyethyl)-2H-pyran-2-one;
 one;
 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(α -ethyl-p-fluorophenethyl)-2H-pyran-2-one;
 5 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(α -ethyl-p-chlorophenethyl)-2H-pyran-2-one;
 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(α -ethyl-m-chlorophenethyl)-2H-pyran-2-one;
 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(α -ethyl-o-chlorophenethyl)-2H-pyran-2-one;
 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(α -ethyl-p-bromophenethyl)-2H-pyran-2-one;
 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(α -ethyl-m-bromophenethyl)-2H-pyran-2-one;
 10 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(α -ethyl-p-trifluoromethylphenethyl)-2H-pyran-2-one;
 one;
 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(α -ethyl-m-trifluoromethylphenethyl)-2H-pyran-2-one;
 one;
 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(α -ethyl-o-trifluoromethylphenethyl)-2H-pyran-2-one;
 15 one;
 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(α -ethyl-p-methoxyphenethyl)-2H-pyran-2-one;
 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(α -ethyl-m-methoxyphenethyl)-2H-pyran-2-one;
 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(p-fluorophenethyl)-2H-pyran-2-one;
 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(p-chlorophenethyl)-2H-pyran-2-one;
 20 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(p-bromophenethyl)-2H-pyran-2-one;
 3-(Cyclopropylphenylmethyl)-6-[1-ethyl-3-(4-morpholinyl)propyl]-4-hydroxy-2H-pyran-2-one;
 3-(Cyclopropylphenylmethyl)- β -ethyl-4-hydroxy-2-oxo-, phenylmethyl ester 2H-pyran-6-propanoic acid;
 25 3-(Cyclopropylphenylmethyl)-4-hydroxy-6-[2-methyl-1-(phenylmethyl)propyl]-2H-pyran-2-one;
 3-(Cyclopropylphenylmethyl)-4-hydroxy-6-[2-methyl-1-[(tetrahydro-2H-pyran-3-yl)methyl]propyl]-2H-pyran-2-one;
 4-Hydroxy-3-(1-phenylpropyl)-6-[1-[(tetrahydro-2H-pyran-3-yl)methyl]propyl]-2H-pyran-2-one;
 30 2-one;
 3-(Cyclopropylphenylmethyl)-6-(1-ethyl-4,4,4-trifluorobutyl)-4-hydroxy-2H-pyran-2-one;
 3-[2-[3-(Cyclopropylphenylmethyl)-4-hydroxy-2-oxo-2H-pyran-6-yl]butyl]-1-[(4-methylphenyl)sulfonyl]-piperidine;
 2-[2-[3-(Cyclopropylphenylmethyl)-4-hydroxy-2-oxo-2H-pyran-6-yl]butyl]-1-[(4-methylphenyl)sulfonyl]-pyrrolidine;
 35 methylphenyl)sulfonyl]-pyrrolidine;
 3-(Cyclopropylphenylmethyl)-4-hydroxy-6-(3,3,3-trifluoropropyl)-2H-pyran-2-one;

- 2-[2-[3-(Cyclopropylphenylmethyl)-4-hydroxy-2-oxo-2H-pyran-6-yl]butyl]-1-[(4-methylphenyl)sulfonyl]-piperidine;
- 4-[2-[3-(Cyclopropylphenylmethyl)-4-hydroxy-2-oxo-2H-pyran-6-yl]butyl]-1-[(4-methylphenyl)sulfonyl]-piperidine;
- 5 4-[2-[3-(Cyclopropylphenylmethyl)-4-hydroxy-2-oxo-2H-pyran-6-yl]butyl]-1-(phenylmethyl)-2-pyrrolidinone;
- 6-(Cyclopentylmethyl)-3-(cyclopropylphenylmethyl)-4-hydroxy-2H-pyran-2-one;
- 3-(Cyclopropylphenylmethyl)-4-hydroxy-6-[(tetrahydro-2H-pyran-4-yl)methyl]-2H-pyran-2-one;
- 10 3-(Cyclopropylphenylmethyl)-6-(3-fluoropropyl)-4-hydroxy-2H-pyran-2-one;
- 4-Hydroxy-3-(1-phenylcyclobutyl)-6-[1-(phenylmethyl)propyl]-2H-pyran-2-one;
- 3-(α -Ethylbenzyl)-6-(α -ethylbenzyl)-4-hydroxy-2H-pyran-2-one;
- 3-(α -Cyclopropyl-*meta*-[(phenylaminocarbonyl)amino]benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 15 3-(α -Cyclopropyl-*meta*-[(4-methoxyphenylaminocarbonyl)amino]benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 3-(α -Cyclopropyl-*meta*-[(benzylaminocarbonyl)amino]benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 3-(α -Cyclopropyl-*meta*-[(4-bromophenylaminocarbonyl)amino]benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 20 3-(α -Cyclopropyl-*meta*-[(phenylsulfonylaminocarbonyl)amino]benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 3-(α -Cyclopropyl-*meta*-(*N*- α -*tert*-butyloxycarbonyl-*N*-im-p-toluenesulfonyl-L-histidylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 25 3-(α -Cyclopropyl-*meta*-(*tert*-butyloxycarbonyl-L-alanyl-amino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 3-(α -Cyclopropyl-*meta*-(4-bromophenylbenzoylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 3-(α -Cyclopropyl-*meta*-(*N*- α -*tert*-butyloxycarbonyl-L-histidylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 30 3-(α -Cyclopropyl-*meta*-(*N*-benzyloxycarbonyl-O- α -benzyl-L-glutamylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 3-(α -Cyclopropyl-*meta*-(4-cyanophenylbenzoylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 35 3-(α -Cyclopropyl-*meta*-(L-glutamylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-

pyran-2-one;

3-(α -Cyclopropyl-*meta*-(3-(1-indolyl)propanoylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;

3-(α -Cyclopropyl-*meta*-(2-pyridylacetyl amino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;

3-(α -Cyclopropylbenzyl)-6-[1-cyclopropylmethyl-2-(tetrahydropyran-3-yl)ethyl]-4-hydroxy-2H-pyran-2-one;

3-(α -Cyclopropyl-*meta*-(3-pyridylacetyl amino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one; and

3-(α -Cyclopropyl-*meta*-(4-pyridylacetyl amino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one.

12. The compound of claim 1

wherein R_1 is $-(CH_2)_n-CH(R_3)-(CH_2)_m-R_4$;

wherein R_2 is hydrogen;

wherein R_3 is $R_4-(CH_2)_m-CH(R_6)-(CH_2)_n$;

wherein R_4 is

a) aryl, or

b) het;

wherein R_5 is C_3 - C_7 cycloalkyl;

wherein R_6 is

a) C_1 - C_{10} alkyl, or

b) $-(CH_2)_n-C_3$ - C_7 cycloalkyl;

wherein aryl is phenyl substituted by zero (0) or one (1) R_8 ;

wherein het is a 5- or 6-membered saturated or unsaturated ring containing from one (1) to four (4) heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring, C_3 - C_8 cycloalkyl, or another heterocycle;

wherein R_8 is

a) $-(CH_2)_n-X_2-CH=CH-R_{12}$,

b) $-(CH_2)_n-X_2-(CH_2)_n-R_{12}$,

c) $-(CH_2)_n-X_2-(CH_2)_n-R_{15}$,

d) $-(CH_2)_n-X_2-C_1$ - C_{10} alkyl substituted by zero (0) or one (1) halo,

e) $-(CH_2)_n-X_2-C_2$ - C_5 alkenyl,

f) $-(CH_2)_n-X_4-N(CH_3)_2$, or

g) $-(CH_2)_n-X_4-NH-R_{12}$;

-276-

wherein X_2 is $-NHSO_2-$;

wherein X_4 is $-NHSO_2-$;

wherein R_{10} and R_{11} taken together form a double bond;

wherein R_{12} is

- 5 a) phenyl substituted by zero (0) to three (3) R_{13} ,
- b) naphthyl substituted by zero (0) to three (3) R_{13} , or
- c) perhalophenyl;

wherein R_{13} is

- a) C_1 - C_{10} alkyl substituted by zero (0) to three (3) halo,
- 10 b) halo,
- c) $-O-C_1-C_5$ alkyl substituted by zero (0) to three (3) halo,
- d) $-CN$,
- e) nitro,
- f) $-COOH$,
- 15 g) $-N(CH_3)_2$,
- h) hydroxy,
- i) $-NHCOCH_3$,
- j) amino,
- k) $-NHOH$,
- 20 l) $-CONH_2$,
- m) $-CH_2NHCO$ -phenyl,
- n) $-SO_2$ -phenyl,
- o) $-N=N$ -phenyl substituted by zero (0) or one (1) $-N(CH_3)_2$, or
- p) $-NHSO_2$ -phenyl;

- 25 wherein R_{15} is a 5- or 6-membered saturated or unsaturated ring containing from one (1) to four (4) heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring, C_3 - C_8 cycloalkyl, or another heterocycle, and substituted by zero (0) to two (2) R_{13} ;

wherein m is zero (0) or one (1);

- 30 wherein n is zero (0) or one (1).

13. The compound of claim 12

wherein R_5 is cyclopropyl;

wherein R_6 is $-(CH_2)_n$ -cyclopropyl or ethyl;

- 35 wherein het is tetrahydropyranyl; and

wherein R_{15} substituted by zero (0) to two (2) R_{13} is

-277-

- a) phthalimidyl,
- b) quinolinyl,
- c) thiophenyl,
- d) pyridyl,
- e) isoxazolyl,
- f) thiophenyl,
- g) imidazolyl,
- h) benzo[1,2,5]oxadiazolyl,
- i) benzo[1,2,5]thiadiazolyl, or
- j) 2-(isoxazol-3-yl)-thiophenyl.

4. The compound of claim 12 selected from the group consisting of:

3-(α -Cyclopropyl-*meta*-(phenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;

3-(α -Cyclopropyl-*meta*-(propylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;

3-(α -Cyclopropyl-*meta*-(*E*)-2-phenylethenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;

3-(α -Cyclopropyl-*meta*-(4-bromophenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;

3-(α -Cyclopropyl-*meta*-(2,5-dichlorophenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;

3-(α -Cyclopropyl-*meta*-(4-*tert*-butylphenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;

3-(α -Cyclopropyl-*meta*-(4-cyanophenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;

3-(α -Cyclopropyl-*meta*-(4-methoxyphenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;

3-(α -Cyclopropyl-*meta*-(4-chlorophenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;

3-(α -Cyclopropyl-*meta*-(8-quinolinesulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;

3-(α -Cyclopropyl-*meta*-(ethylsulfonylamino)benzyl)-6-[1-cyclopropylmethyl-2-(tetrahydropyran-3-yl)ethyl]-4-hydroxy-2H-pyran-2-one;

3-(α -Cyclopropyl-*meta*-(4-methylphenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-

- hydroxy-2H-pyran-2-one;
- 3-(α -Cyclopropyl-*meta*-(4-methylphenylsulfonylamino)benzyl)-6-[1-cyclopropylmethyl-2-(tetrahydropyran-3-yl)ethyl]-4-hydroxy-2H-pyran-2-one;
- 3-(α -Cyclopropyl-*meta*-(ethylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 5 3-(α -Cyclopropyl-*meta*-(4-fluorophenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 3-(α -Cyclopropyl-*meta*-(benzothiadiazolyl-sulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 10 3-(α -Cyclopropyl-*meta*-(benzo-oxadiazolyl-sulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 3-(α -Cyclopropyl-*meta*-((1-methyl-imidazol-4-yl)-sulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 3-(α -Cyclopropyl-*meta*-((pyridine-3-yl)-sulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 15 3-(α -Cyclopropyl-*meta*-(5-(pyridine-2-yl)-thiophene-2-yl-sulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 3-(α -Cyclopropyl-*meta*-(4-hydroxyaminophenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 20 3-(α -Cyclopropyl-*meta*-(4-dimethylaminophenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 3-(α -Cyclopropyl-*meta*-(3-aminophenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 3-(α -Cyclopropyl-*meta*-(4-aminocarbonylphenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 25 3-(α -Cyclopropylbenzyl)-6-(α -ethylphenylsulfonylaminomethyl)-4-hydroxy-2H-pyran-2-one;
- 3-(α -Cyclopropylbenzyl)-6-(1-ethyl-2-phenylsulfonylamino-ethyl)-4-hydroxy-2H-pyran-2-one;
- 30 3-(α -Cyclopropyl-*meta*-(4-fluorophenylsulfonylamino)benzyl)-6-(α -ethylphenylsulfonylaminomethyl)-4-hydroxy-2H-pyran-2-one;
- 3-(α -Cyclopropyl-*meta*-(phenylsulfonylamino)benzyl)-6-(α -ethylphenylsulfonylaminomethyl)-4-hydroxy-2H-pyran-2-one;
- 3-(α -Cyclopropyl-*meta*-(2,5-dichlorophenylsulfonylamino)benzyl)-6-(α -ethyl-

-279-

- phenylsulfonylaminomethyl)-4-hydroxy-2H-pyran-2-one;
 3-(α -Cyclopropyl-*meta*-(4-cyanophenylsulfonylamino)benzyl)-6-(α -ethyl-phenylsulfonylaminomethyl)-4-hydroxy-2H-pyran-2-one;
 3-(α -Cyclopropyl-*meta*-(quinolin-8-yl-sulfonylamino)benzyl)-6-(α -ethyl-phenylsulfonylaminomethyl)-4-hydroxy-2H-pyran-2-one;
 5 3-(α -Cyclopropyl-*meta*-(2-phenylethenyl)-sulfonylamino)benzyl)-6-(α -ethyl-phenylsulfonylaminomethyl)-4-hydroxy-2H-pyran-2-one;
 3-(α -Cyclopropyl-*meta*-((1-methyl-imidazo-4-yl)-sulfonylamino)benzyl)-6-(α -ethyl-phenylsulfonylaminomethyl)-4-hydroxy-2H-pyran-2-one;
 10 3-(α -Cyclopropyl-*meta*-(pyridin-3-yl-sulfonylamino)benzyl)-6-(α -ethyl-phenylsulfonylaminomethyl)-4-hydroxy-2H-pyran-2-one;
 3-(α -Cyclopropyl-*meta*-(4-dimethylamino-phenylsulfonylamino)benzyl)-6-(α -ethyl-phenylsulfonylaminomethyl)-4-hydroxy-2H-pyran-2-one;
 3-(α -Cyclopropyl-*meta*-(4-fluorophenylsulfonylamino)benzyl)-6-(1-ethyl-2-phenylsulfonylamino-ethyl)-4-hydroxy-2H-pyran-2-one;
 15 3-(α -Cyclopropyl-*meta*-(phenylsulfonylamino)benzyl)-6-(1-ethyl-2-phenylsulfonylamino-ethyl)-4-hydroxy-2H-pyran-2-one;
 3-(α -Cyclopropyl-*meta*-(2,5-dichlorophenylsulfonylamino)benzyl)-6-(1-ethyl-2-phenylsulfonylamino-ethyl)-4-hydroxy-2H-pyran-2-one;
 20 3-(α -Cyclopropyl-*meta*-(4-cyanophenylsulfonylamino)benzyl)-6-(1-ethyl-2-phenylsulfonylamino-ethyl)-4-hydroxy-2H-pyran-2-one;
 3-(α -Cyclopropyl-*meta*-(quinolin-8-yl-sulfonylamino)benzyl)-6-(1-ethyl-2-phenylsulfonylamino-ethyl)-4-hydroxy-2H-pyran-2-one;
 3-(α -Cyclopropyl-*meta*-(2-phenylethenyl)-sulfonylamino)benzyl)-6-(1-ethyl-2-phenylsulfonylamino-ethyl)-4-hydroxy-2H-pyran-2-one;
 25 3-(α -Cyclopropyl-*meta*-((1-methyl-imidazo-4-yl)-sulfonylamino)benzyl)-6-(1-ethyl-2-phenylsulfonylamino-ethyl)-4-hydroxy-2H-pyran-2-one;
 3-(α -Cyclopropyl-*meta*-(pyridin-3-yl-sulfonylamino)benzyl)-6-(1-ethyl-2-phenylsulfonylamino-ethyl)-4-hydroxy-2H-pyran-2-one; and
 30 3-(α -Cyclopropyl-*meta*-(4-dimethylamino-phenylsulfonylamino)benzyl)-6-(1-ethyl-2-phenylsulfonylamino-ethyl)-4-hydroxy-2H-pyran-2-one.

15. The compound of claim 1

wherein R₁ is

- 35 a) $-(CH_2)_n-CH(R_5)-(CH_2)_m-R_4$, or

-280-

b) $-\text{CH}(\text{R}_5)-\text{S}-(\text{CH}_2)_m-\text{R}_4$;wherein R_2 is

a) hydrogen, or

b) $-\text{C}_1-\text{C}_6$ alkyl;5 wherein R_3 isa) $\text{R}_4-(\text{CH}_2)_m-\text{CH}(\text{R}_6)-(\text{CH}_2)_n-$,b) $\text{R}_4-\text{CH}(\text{R}_6)-\text{CH}(\text{R}_6)-$,c) $\text{R}_{12}-(\text{CH}_2)_m-\text{X}_2-(\text{CH}_2)_n-(\text{R}_7)\text{HC}-$, ord) $\text{R}_{15}-(\text{CH}_2)_m-\text{X}_2-(\text{CH}_2)_n-(\text{R}_7)\text{HC}$;10 wherein R_4 is

a) aryl, or

b) het;

wherein R_5 isa) C_1-C_4 alkyl, or

15 b) cyclopropyl;

wherein R_6 isa) C_1-C_4 alkyl,b) $-\text{CH}_2$ -cyclopropyl, or

c) hydroxy;

20 wherein R_7 is

a) hydrogen, or

b) C_1-C_5 alkyl;wherein aryl is phenyl substituted by zero (0) or two (2) R_8 ;

wherein het is

25 a) furan-2-yl substituted by zero (0) or two (2) R_9 ,b) furan-3-yl substituted by zero (0) or two (2) R_9 ,c) thiophen-2-yl substituted by zero (0) or two (2) R_9 ,d) thiophen-3-yl substituted by zero (0) or two (2) R_9 ,e) tetrahydrofuran-2-yl substituted by zero (0) or two (2) R_9 ,30 f) tetrahydrofuran-3-yl substituted by zero (0) or two (2) R_9 ,g) tetrahydropyran-2-yl substituted by zero (0) or two (2) R_9 ,h) tetrahydropyran-3-yl substituted by zero (0) or two (2) R_9 , or

i) 8-quinoliny;

wherein R_8 and R_9 are independently35 a) C_1-C_8 alkyl,

b) halo,

-281-

- c) hydroxy-C₁-C₄ alkyl,
- d) -(CH₂)_n-X₂-(CH₂)_n-R₁₂,
- e) -(CH₂)_n-X₂-(CH₂)_n-R₁₅;

wherein X₂ is

- 5 a) -NHSO₂-,
- b) -SO₂NH-, or
- c) -NHC(O)-;

wherein R₁₀ and R₁₁ taken together form a double bond;

wherein R₁₂ is phenyl substituted by zero (0) to three (3) R₁₃;

10 wherein R₁₃ is

- a) C₁-C₆ alkyl,
- b) hydroxy,
- c) hydroxy-C₁-C₅ alkyl,
- d) halo,
- 15 e) -CN, or
- f) amino;

wherein R₁₅ is

- a) thiophen-2-yl substituted by zero (0) to three (3) R₁₃,
- b) thiophen-3-yl substituted by zero (0) to three (3) R₁₃,
- 20 c) quinolin-8-yl substituted by zero (0) to three (3) R₁₃,
- d) furan-2-yl substituted by zero (0) to three (3) R₁₃, or
- e) furan-3-yl substituted by zero (0) to three (3) R₁₃;

wherein m is zero (0) to four (4), inclusive;

wherein n is zero (0) to four (4), inclusive.

25

16. The compound of claim 15 selected from the group consisting of

N-[5-[α[R]-Cyclopropyl-α-[6-(α[R]-ethyl-α[S]-tetrahydrofuran-2-ylmethyl)methyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide;

N-[5-[α[R]-Cyclopropyl-α-[6-(α[R]-ethyl-α[R]-tetrahydrofuran-2-ylmethyl)methyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide;

N-[5-[α[R]-Cyclopropyl-α-[6-(α[R]-ethyl-α[S]-tetrahydrofuran-2-ylmethyl)methyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-fluorophenylsulfonamide;

N-[5-[α[R]-Cyclopropyl-α-[6-(α[R]-ethyl-α[R]-tetrahydrofuran-2-ylmethyl)methyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-fluorophenylsulfonamide;

35 N-[5-[α[R]-Cyclopropyl-α-[6-(1[S]-ethyl-2[R]-hydroxy-2-[S]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide;

N-[5-[α [R]-Cyclopropyl- α -[6-(1[S]-ethyl-2[R]-hydroxy-2-[R]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide;

N-[5-[α [R]-Cyclopropyl- α -[6-(1[R]-ethyl-2[S]-hydroxy-2-[S]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide;

5 N-[5-[α [R]-Cyclopropyl- α -[6-(1[R]-ethyl-2[S]-hydroxy-2-[R]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide;

N-[5-[α [R]-Cyclopropyl- α -[6-(1[S]-ethyl-2[S]-hydroxy-2-[S]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide;

10 N-[5-[α [R]-Cyclopropyl- α -[6-(1[S]-ethyl-2[S]-hydroxy-2-[R]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide;

N-[5-[α [R]-Cyclopropyl- α -[6-(1[R]-ethyl-2[R]-hydroxy-2-[S]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide;

N-[5-[α [R]-Cyclopropyl- α -[6-(1[R]-ethyl-2[R]-hydroxy-2-[R]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide;

15 N-[5-[α [S]-Cyclopropyl- α -[6-(1[S]-ethyl-2[R]-hydroxy-2-[S]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide;

N-[5-[α [S]-Cyclopropyl- α -[6-(1[S]-ethyl-2[R]-hydroxy-2-[R]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide;

20 N-[5-[α [S]-Cyclopropyl- α -[6-(1[R]-ethyl-2[S]-hydroxy-2-[S]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide;

N-[5-[α [S]-Cyclopropyl- α -[6-(1[R]-ethyl-2[S]-hydroxy-2-[R]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide;

N-[5-[α [S]-Cyclopropyl- α -[6-(1[S]-ethyl-2[S]-hydroxy-2-[S]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide;

25 N-[5-[α [S]-Cyclopropyl- α -[6-(1[S]-ethyl-2[S]-hydroxy-2-[R]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide;

N-[5-[α [S]-Cyclopropyl- α -[6-(1[R]-ethyl-2[R]-hydroxy-2-[S]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide;

30 N-[5-[α [S]-Cyclopropyl- α -[6-(1[R]-ethyl-2[R]-hydroxy-2-[R]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide;

3-(α [S]-Cyclopropyl(5-(2-hydroxyethyl))thiophen-2-ylmethyl)-6-(1[R]-ethyl-2-[R]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2H-pyran-2-one;

3-(α [S]-Cyclopropyl(5-(2-hydroxyethyl))thiophen-2-ylmethyl)-6-(α [R]-ethylphenethyl)-4-hydroxy-2H-pyran-2-one;

35 3-(α [S]-Cyclopropyl(5-(2-hydroxyethyl))thiophen-2-ylmethyl)-6-(α [R]-ethyl-meta-hydroxymethylphenethyl)-4-hydroxy-2H-pyran-2-one;

- 3-(α [S]-Cyclopropyl(5-(2-hydroxyethyl))thiophen-2-ylmethyl)-6-(α [R]-ethyl-ortho-hydroxymethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 3-(α [S]-Cyclopropyl(5-(1,2-dihydroxyethyl))thiophen-2-ylmethyl)-6-(1[R]-ethyl-2-[R]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2H-pyran-2-one;
- 5 3-(α [S]-Cyclopropyl(5-(1,2-dihydroxyethyl))thiophen-2-ylmethyl)-6-(α [R]-ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 3-(α [S]-Cyclopropyl(5-(1,2-dihydroxyethyl))thiophen-2-ylmethyl)-6-(α [R]-ethyl-meta-hydroxymethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 3-(α [S]-Cyclopropyl(5-(1,2-dihydroxyethyl))thiophen-2-ylmethyl)-6-(α [R]-ethyl-ortho-
- 10 hydroxymethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 3-(α [S]-Cyclopropyl)-meta-(4-cyanophenylsulfonylamino)benzyl)-6-(α [R]-ethylphenethyl-4-hydroxy-2H-pyran-2-one;
- 3-(α [S]-Cyclopropyl)-meta-(4-cyanophenylsulfonylamino)benzyl)-6-(α [S]-ethylphenethyl-4-hydroxy-2H-pyran-2-one;
- 15 3-(α [R]-Cyclopropyl)-meta-(4-cyanophenylsulfonylamino)benzyl)-6-(α [S]-ethylphenethyl-4-hydroxy-2H-pyran-2-one;
- 3-(α [R]-Cyclopropyl)-meta-(4-cyanophenylsulfonylamino)benzyl)-6-(α [R]-ethylphenethyl-4-hydroxy-2H-pyran-2-one;
- 3-[(R)-Cyclopropylmethyl(5-N-(p-fluorophenylsulfonyl)methyl)thiophenemercapto-2-
- 20 yl)-6-(α [R]-ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- N-[5-(α [R]-Ethyl- α -[6-(α [R]-ethyl- α [S]-tetrahydrofuran-2-ylmethyl)methyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide;
- N-[5-(α [R]-Ethyl- α -[6-(α [R]-ethyl- α [R]-tetrahydrofuran-2-ylmethyl)methyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide;
- 25 N-[5-(α [R]-Ethyl- α -[6-(α [R]-ethyl- α [S]-tetrahydrofuran-2-ylmethyl)methyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-fluorophenylsulfonamide;
- N-[5-(α [R]-Ethyl- α -[6-(α [R]-ethyl- α [R]-tetrahydrofuran-2-ylmethyl)methyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-fluorophenylsulfonamide;
- N-[5-(α [R]-Ethyl- α -[6-(1[S]-ethyl-2[R]-hydroxy-2-[S]tetrahydrofuran-2-yl)ethyl-4-
- 30 hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide;
- N-[5-(α [R]-Ethyl- α -[6-(1[S]-ethyl-2[R]-hydroxy-2-[R]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide;
- N-[5-(α [R]-Ethyl- α -[6-(1[R]-ethyl-2[S]-hydroxy-2-[S]tetrahydrofuran-2-yl)ethyl-4-
- hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide;
- 35 N-[5-(α [R]-Ethyl- α -[6-(1[R]-ethyl-2[S]-hydroxy-2-[R]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide;

- N-[5-[α (R)-Ethyl- α -[6-(1[S]-ethyl-2[S]-hydroxy-2-[S]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide;
- N-[5-[α (R)-Ethyl- α -[6-(1[S]-ethyl-2[S]-hydroxy-2-[R]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide;
- 5 N-[5-[α (R)-Ethyl- α -[6-(1[R]-ethyl-2[R]-hydroxy-2-[S]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide;
- N-[5-[α (R)-Ethyl- α -[6-(1[R]-ethyl-2[R]-hydroxy-2-[R]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide;
- 10 N-[5-[α (S)-Ethyl- α -[6-(1[S]-ethyl-2[R]-hydroxy-2-[S]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide;
- N-[5-[α (S)-Ethyl- α -[6-(1[S]-ethyl-2[R]-hydroxy-2-[R]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide;
- N-[5-[α (S)-Ethyl- α -[6-(1[R]-ethyl-2[S]-hydroxy-2-[S]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide;
- 15 N-[5-[α (S)-Ethyl- α -[6-(1[R]-ethyl-2[S]-hydroxy-2-[R]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide;
- N-[5-[α (S)-Ethyl- α -[6-(1[S]-ethyl-2[S]-hydroxy-2-[S]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide;
- 20 N-[5-[α (S)-Ethyl- α -[6-(1[R]-ethyl-2[R]-hydroxy-2-[S]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide; and
- N-[5-[α (S)-Ethyl- α -[6-(1[R]-ethyl-2[R]-hydroxy-2-[R]tetrahydrofuran-2-yl)ethyl-4-hydroxy-2-pyran-3-yl]-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide.
- 25 17. The compound of claim 1 selected from the group consisting of:
- 3-(α -Cyclopropyl-*meta*-(benzyloxycarbonylamino)benzyl)-6-(α -ethyl-phenethyl)-4-hydroxy-2H-pyran-2-one;
- 3-(α -Cyclopropyl-*meta*-(*tert*-butoxycarbonylamino)benzyl)-6-(α -cyclopropylmethyl-
- 30 cyclopropylethyl)-4-hydroxy-2H-pyran-2-one;
- 4-Hydroxy-3-(1-phenyl-propyl)-6-(1-propyl-butyl)-pyran-2-one;
- 4-Hydroxy-3-(1-phenyl-allyl)-6-(1-propyl-butyl)-pyran-2-one;
- 3-(5-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-oxo-6H-pyran-2-yl)-propionic acid *tert*-butyl ester;
- 35 3-(Cyclopropyl-phenyl-methyl)-6-(2-(3,5-dimethyl-isoxazol-4-yl)-ethyl)-4-hydroxy-pyran-2-one;

- 6-(2-(5-tert-Butyl-(1,2,4)oxadiazol-3-yl)-ethyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one;
- 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(2-phenyl-1-pyridin-2-ylmethyl-ethyl)-pyran-2-one;
- 5 3-(Cyclopropyl-phenyl-methyl)-6-(2-(1,3)dioxolan-2-yl-ethyl)-4-hydroxy-pyran-2-one;
- 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(4-morpholin-4-yl-butyl)-pyran-2-one;
- 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(2-pyridin-2-yl-ethyl)-pyran-2-one;
- 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(2-(2-methyl-thiazol-4-yl)-ethyl)-pyran-2-one;
- 10 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(2-quinolin-2-yl-ethyl)-pyran-2-one;
- 6-(3-Chloro-propyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one;
- 6-(1-(2-(4-Chloro-phenyl)-thiazol-4-ylmethyl)-propyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one;
- 3-(Cyclopropyl-phenyl-methyl)-6-(3-(1,3)dioxan-2-yl-1-ethyl-propyl)-4-hydroxy-pyran-2-one;
- 15 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(1-pyridin-4-ylmethyl-propyl)-pyran-2-one;
- 3-(Cyclopropyl-phenyl-methyl)-6-(1-ethyl-3-morpholin-4-yl-3-oxo-propyl)-4-hydroxy-pyran-2-one;
- 3-(Cyclopropyl-phenyl-methyl)-6-(1-ethyl-4-morpholin-4-yl-butyl)-4-hydroxy-pyran-2-one;
- 20 3-(Cyclopropyl-phenyl-methyl)-6-[1-(2,3-dihydro-benzo[1,4]dioxin-2-ylmethyl)-propyl]-4-hydroxy-pyran-2-one;
- 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-isobutyl-pyran-2-one;
- Cyclopropyl-phenyl-methyl)-6-[1-(5,6-dihydro-2H-pyran-3-ethyl)-propyl]-4-hydroxy-pyran-2-one;
- 25 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-5-(2-(2-methoxy-ethoxy)-ethyl)-6-propyl-pyran-2-one;
- 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(1-isobutyl-3-methyl-butyl)-pyran-2-one;
- 3-Dicyclopropylmethyl-4-hydroxy-6-phenethyl-pyran-2-one;
- 30 6-(1-Cyclopropyl-ethyl)-3-dicyclopropylmethyl-4-hydroxy-pyran-2-one;
- 6-(1-Cyclopropyl-1-cyclopropylmethyl-ethyl)-3-dicyclopropylmethyl-4-hydroxy-pyran-2-one;
- 6-(1-Cyclohexylmethyl-propyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one;
- 6-(1-Benzyl-propyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one;
- 35 6-(2-Cyclopropyl-1-cyclopropylmethyl-ethyl)-4-hydroxy-3(1-phenyl-propyl)-pyran-2-one;
- 6-(1-Benzyl-2-cyclopropyl-ethyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one;

-286-

- 6-(2-Cyclopropyl-ethyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one;
 6-(1-Cyclopropylmethyl-propyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one;
 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(4-phenyl-butyl)-pyran-2-one;
 3-(Cyclohexyl-cyclopropyl-methyl)-6-(2-cyclopropyl-1-cyclopropylmethyl-ethyl)-4-
 5 hydroxy-pyran-2-one;
 3-(Cyclopropyl-phenyl-methyl)-6-(1-ethyl-4-phenyl-butyl)-4-hydroxy-pyran-2-one;
 6-(3-Cyclohexyl-propyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one;
 6-(3-Cyclohexyl-1-ethyl-propyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one;
 6-(2-Cyclopropyl-ethyl)-4-hydroxy-3-(1-phenyl-propyl)-pyran-2-one;
 10 6-But-3-enyl-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one;
 3-(Cyclopropyl-phenyl-methyl)-6-(1-ethyl-3-phenyl-propyl)-4-hydroxy-pyran-2-one;
 5-Bromo-6-(2-cyclopropyl-ethyl)-4-hydroxy-3-(1-phenyl-propyl)-pyran-2-one;
 6-(1-Benzyl-2-phenyl-ethyl)-4-hydroxy-3-(1-phenyl-propyl)-pyran-2-one;
 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(3-(2-methoxy-ethoxy)-propyl)-pyran-2-one;
 15 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-5-(2-(2-methoxy-ethoxy)-ethyl)-6-(3-(2-
 methoxy-ethoxy)-pyran-2-one;
 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-propyl-pyran-2-one;
 5-Bromo-4-hydroxy-6-phenylethyl-3-(1-phenyl-propyl)-pyran-2-one;
 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(3-(2-methoxy-ethoxy)-ethoxy)-propyl-
 20 pyran-2-one;
 5-Bromo-4-hydroxy-3-(1-phenyl-propyl)-6-propyl-pyran-2-one;
 3-(Cyclopropyl-phenyl-methyl)-6-(1-ethyl-propyl)-4-hydroxy-5-(2-(2-methoxy-
 ethoxy)ethyl)-pyran-2-one;
 6-(1-Benzyl-propyl)-5-bromo-4-hydroxy-3-(1-phenyl-propyl)-pyran-2-one;
 25 6-(2-Cyclopropyl-1-cyclopropylmethyl-ethyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-
 5-(2-(2-methoxy-ethoxy)-ethoxy)-ethyl)-pyran-2-one;
 3-(Cyclopropyl-phenyl-methyl)-6-(2-furan-2-yl-2-hydroxy-ethyl)-4-hydroxy-pyran-2-one;
 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(4,4,4-trifluoro-butyl)-pyran-2-one;
 6-[2-(1-Cyclohexyl-1H-tetrazol-5-yl)-ethyl]-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-2-
 30 one; and
 4-Hydroxy-3-(1-phenyl-propyl)-1-oxa-spiro[5.5]undec-3-ene-2,9-dione monooxime.

18. The compound of claim 1 selected from the group consisting of:

- 3-([R]- α -ethylbenzyl)-4-hydroxy-6-([R]- α -ethylphenethyl)-2H-pyran-2-one;
 35 3-([R]- α -ethylbenzyl)-4-hydroxy-6-([S]- α -ethylphenethyl)-2H-pyran-2-one;
 3-([S]- α -ethylbenzyl)-4-hydroxy-6-([R]- α -ethylphenethyl)-2H-pyran-2-one;

- 3-([S]- α -ethylbenzyl)-4-hydroxy-6-([S]- α -ethylphenethyl)-2H-pyran-2-one;
3-(α -cyclopropyl((5-methoxymethylhydroxymethylether)furfur-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one;
3-(α -cyclopropyl((5-hydroxymethyl)furfur-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one;
5 3-(α -cyclopropyl((5-methoxymethyl)furfur-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one;
3-(α -cyclopropyl((5-azidomethyl)furfur-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one;
10 3-(α -cyclopropyl((5-aminomethyl)furfur-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one;
3-(α -cyclopropyl((5-[N-acetyl]aminomethyl)furfur-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one;
3-(α -cyclopropyl((5-[N-phenylsulphonyl]aminomethyl)furfur-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one;
15 3-(α -cyclopropyl((5-[N-(o-fluoro)phenylsulphonyl]aminomethyl)furfur-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one;
3-(α -cyclopropyl((5-[N-(p-fluoro)phenylsulphonyl]aminomethyl)furfur-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one;
20 3-(α -cyclopropyl((5-[N-(m-fluoro)phenylsulphonyl]aminomethyl)furfur-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one;
3-(α -cyclopropyl((5-[N-(m-fluoro)phenylsulphonyl]aminomethyl)furfur-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one;
3-(α -cyclopropyl((5-[N-(o-cyano)phenylsulphonyl]aminomethyl)furfur-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one;
25 3-(α -cyclopropyl((5-[N-(p-cyano)phenylsulphonyl]aminomethyl)furfur-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one;
3-(α -cyclopropyl((5-[N-(m-cyano)phenylsulphonyl]aminomethyl)furfur-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one;
30 3-(α -cyclopropyl((5-[N-(m-cyano)phenylsulphonyl]aminomethyl)furfur-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one;
3-(α -cyclopropyl((5-(4-carboethoxy-1,2,3-triazol-1-yl)methyl)furfur-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one;
3-(α -cyclopropyl((5-(4-carboxylic-1,2,3-triazol-1-yl)methyl)furfur-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one;
35 3-(α -cyclopropyl((5-(1-nitro-2-methylthioethen-2-yl)aminomethyl)furfur-2-yl))-4-

- hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one;
 3-(α -cyclopropyl((5-(N-(1-nitro-2-[N-isopropyl])ethen-2-yl)aminomethyl)furfur-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one;
 3-(α -cyclopropyl((5-(N-(N-cyano, methylthioimino)aminomethyl)furfur-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one;
 5 6-(α -ethylphenethyl)-2H-pyran-2-one;
 3-(α -cyclopropyl((5-(N-(N-cyano, N'-isopropylguanidine)aminomethyl)furfur-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one;
 3-(α -cyclopropyl((5-(N-benzylcarbamate)aminomethyl)furfur-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one;
 10 3-(α -cyclopropyl((5-(N-benzylcarbamate)aminomethyl)thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one;
 3-(α -cyclopropyl((5-aminomethyl)thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one;
 3-(α -cyclopropyl((5-(N-phenylsulphonyl)aminomethyl)thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one;
 15 6-(α -ethylphenethyl)-2H-pyran-2-one;
 3-(α -cyclopropylfurfur-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one;
 3-(α -cyclopropyl(5-N-phenylsulphonyl)furfur-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one;
 3-(α -cyclopropyl((5-methoxymethylhydroxymethylether)thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one;
 20 hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one;
 3-(α -cyclopropyl((5-hydroxymethyl)thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one;
 3-(α -cyclopropyl((5-methoxymethyl)thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one;
 25 3-(α -cyclopropyl((5-azidomethyl)thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one;
 3-(α -cyclopropyl((5-aminomethyl)thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one;
 3-(α -cyclopropyl((5-[N-acetyl]aminomethyl)thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one;
 30 ethylphenethyl)-2H-pyran-2-one;
 3-(α -cyclopropyl((5-[N-phenylsulphonyl]aminomethyl)thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one;
 3-(α -cyclopropyl((5-(4-carboethoxy-1,2,3-triazol-1-yl)methyl)thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one;
 35 3-(α -cyclopropyl((5-(4-carboxylic-1,2,3-triazol-1-yl)methyl)thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one;

- 3-(α -cyclopropyl((5-(N-(1-nitro-2-methylthioethen-2-ylmethyl)aminomethyl)thiophen-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one;
- 3-(α -cyclopropyl((5-(N-(1-nitro-2-[N-isopropyl]ethen-2-yl)aminomethyl)thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one;
- 5 3-(α -cyclopropyl((5-(N-(N-cyano, methylthioimino)aminomethyl)thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one;
- 3-(α -cyclopropyl((5-(N-(N-cyano, N'-isopropylguanidine)aminomethyl)thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one;
- 10 3-(α -cyclopropylthiophen-2-ylmethyl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one;
- 3-(α -cyclopropyl(5-N-phenylsulphonyl)thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one;
- 3-(α [S]-Ethylbenzyl)-4-hydroxy-6-(α [R]-ethyl- β [S]-hydroxyphenethyl)-2H-pyran-2-one;
- 3-(α [S]-Ethylbenzyl)-4-hydroxy-6-(α [S]-ethyl- β [R]-hydroxyphenethyl)-2H-pyran-2-one;
- 3-(α [S]-Ethylbenzyl)-4-hydroxy-6-(α [R]-ethyl- β [R]-hydroxyphenethyl)-2H-pyran-2-one;
- 15 3-(α [S]-Ethylbenzyl)-4-hydroxy-6-(α [S]-ethyl- β [S]-hydroxyphenethyl)-2H-pyran-2-one;
- 3-(α [R]-Ethylbenzyl)-4-hydroxy-6-(α [R]-ethyl- β [S]-hydroxyphenethyl)-2H-pyran-2-one;
- 3-(α [R]-Ethylbenzyl)-4-hydroxy-6-(α [S]-ethyl- β [R]-hydroxyphenethyl)-2H-pyran-2-one;
- 3-(α [R]-Ethylbenzyl)-4-hydroxy-6-(α [R]-ethyl- β [R]-hydroxyphenethyl)-2H-pyran-2-one;
- 3-(α [R]-Ethylbenzyl)-4-hydroxy-6-(α [S]-ethyl- β [S]-hydroxyphenethyl)-2H-pyran-2-one;
- 20 3-(α [S]-Cyclopropylbenzyl)-4-hydroxy-6-(α [R]-ethyl- β [S]-hydroxyphenethyl)-2H-pyran-2-one;
- 3-(α [S]-Cyclopropylbenzyl)-4-hydroxy-6-(α [S]-ethyl- β [R]-hydroxyphenethyl)-2H-pyran-2-one;
- 3-(α [S]-Cyclopropylbenzyl)-4-hydroxy-6-(α [R]-ethyl- β [R]-hydroxyphenethyl)-2H-pyran-2-one;
- 25 3-(α [S]-Cyclopropylbenzyl)-4-hydroxy-6-(α [S]-ethyl- β [S]-hydroxyphenethyl)-2H-pyran-2-one;
- 3-(α [R]-Cyclopropylbenzyl)-4-hydroxy-6-(α [R]-ethyl- β [S]-hydroxyphenethyl)-2H-pyran-2-one;
- 3-(α [R]-Cyclopropylbenzyl)-4-hydroxy-6-(α [S]-ethyl- β [R]-hydroxyphenethyl)-2H-pyran-2-one;
- 30 3-(α [R]-Cyclopropylbenzyl)-4-hydroxy-6-(α [R]-ethyl- β [R]-hydroxyphenethyl)-2H-pyran-2-one; and
- 3-(α [R]-Cyclopropylbenzyl)-4-hydroxy-6-(α [S]-ethyl- β [S]-hydroxyphenethyl)-2H-pyran-2-one.
- 35 2-one.

19. The compound of claim 1 selected from the group consisting of:
- 3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one;
- 3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(α -ethyl-[p-fluorophenethyl])-2H-pyran-2-one;
- 3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(α -ethyl-[p-chlorophenethyl])-2H-pyran-2-one;
- 5 3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(α -ethyl-[p-bromophenethyl])-2H-pyran-2-one;
- 3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(α -ethyl-[p-methylphenethyl])-2H-pyran-2-one;
- 3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(α -ethyl-[p-methoxyphenethyl])-2H-pyran-2-one;
- 3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(α -ethyl-[p-hydroxyphenethyl])-2H-pyran-2-one;
- 3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(α -ethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-
- 10 one;
- 3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(α -ethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-
- one;
- 3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-fluorophenethyl])-2H-
- pyran-2-one;
- 15 3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-chlorophenethyl])-2H-
- pyran-2-one;
- 3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-bromophenethyl])-2H-
- pyran-2-one;
- 3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-methylphenethyl])-2H-
- 20 pyran-2-one;
- 3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-methoxyphenethyl])-2H-
- pyran-2-one;
- 3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-hydroxyphenethyl])-2H-
- pyran-2-one;
- 25 3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-trifluoromethylphenethyl])-
- 2H-pyran-2-one;
- 3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-trifluoromethylphenethyl])-
- 2H-pyran-2-one;
- 3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(1-(tetrahydrofuran-2-ylmethyl)propyl)-2H-pyran-2-
- 30 one;
- 3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(1-(tetrahydrofuran-3-ylmethyl)propyl)-2H-pyran-2-
- one;
- 3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(1-(tetrahydrofuran-2-ylmethyl)cyclopropylmethyl)-
- 2H-pyran-2-one;
- 35 3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(1-(tetrahydrofuran-3-ylmethyl)cyclopropylmethyl)-
- 2H-pyran-2-one;

- 3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(1-(tetrahydropyran-2-ylmethyl)propyl)-2H-pyran-2-one;
- 3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(1-(tetrahydropyran-3-ylmethyl)propyl)-2H-pyran-2-one;
- 5 3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(1-(tetrahydropyran-4-ylmethyl)propyl)-2H-pyran-2-one;
- 3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(1-(tetrahydropyran-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
- 3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(1-(tetrahydropyran-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
- 10 2H-pyran-2-one;
- 3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(1-(tetrahydropyran-4-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
- 3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(1-(furan-2-ylmethyl)propyl)-2H-pyran-2-one;
- 3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(1-(furan-3-ylmethyl)propyl)-2H-pyran-2-one;
- 15 3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(1-(thiophen-2-ylmethyl)propyl)-2H-pyran-2-one;
- 3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(1-(thiophen-3-ylmethyl)propyl)-2H-pyran-2-one;
- 3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(1-(furan-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
- 3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(1-(furan-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
- 20 2H-pyran-2-one;
- 3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(1-(thiophen-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
- 3-(α -ethyl(furfur-2-yl))-4-hydroxy-6-(1-(thiophen-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
- 25 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one;
- 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(α -ethyl-[p-fluorophenethyl])-2H-pyran-2-one;
- 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(α -ethyl-[p-chlorophenethyl])-2H-pyran-2-one;
- 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(α -ethyl-[p-bromophenethyl])-2H-pyran-2-one;
- 30 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(α -ethyl-[p-methylphenethyl])-2H-pyran-2-one;
- 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(α -ethyl-[p-methoxyphenethyl])-2H-pyran-2-one;
- 35 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(α -ethyl-[p-hydroxyphenethyl])-2H-pyran-2-one;

- one;
- 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(α -ethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-one;
- 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(α -ethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-one;
- 5 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-fluorophenethyl])-2H-pyran-2-one;
- 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-chlorophenethyl])-2H-pyran-2-one;
- 10 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-bromophenethyl])-2H-pyran-2-one;
- 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-methylphenethyl])-2H-pyran-2-one;
- 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-methoxyphenethyl])-2H-pyran-2-one;
- 15 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-hydroxyphenethyl])-2H-pyran-2-one;
- 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-one;
- 20 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-one;
- 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(1-(tetrahydrofuran-2-ylmethyl)propyl)-2H-pyran-2-one;
- 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(1-(tetrahydrofuran-3-ylmethyl)propyl)-2H-pyran-2-one;
- 25 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(1-(tetrahydrofuran-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
- 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(1-(tetrahydrofuran-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
- 30 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(1-(tetrahydropyran-2-ylmethyl)propyl)-2H-pyran-2-one;
- 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(1-(tetrahydropyran-3-ylmethyl)propyl)-2H-pyran-2-one;
- 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(1-(tetrahydropyran-4-ylmethyl)propyl)-2H-pyran-2-one;
- 35 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(1-(tetrahydropyran-2-

- ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(1-(tetrahydropyran-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(1-(tetrahydropyran-4-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
 5 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(1-(furan-2-ylmethyl)propyl)-2H-pyran-2-one;
 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(1-(furan-3-ylmethyl)propyl)-2H-pyran-2-one;
 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(1-(thiophen-2-ylmethyl)propyl)-2H-pyran-2-one;
 one;
 10 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(1-(thiophen-3-ylmethyl)propyl)-2H-pyran-2-one;
 one;
 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(1-(furan-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(1-(furan-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
 15 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(1-(thiophen-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
 3-(α -cyclopropyl(furfur-2-yl))-4-hydroxy-6-(1-(thiophen-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
 20 3-(α -ethyl(5-methyl(furfur-2-yl)))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one;
 3-(α -ethyl(5-methyl(furfur-2-yl)))-4-hydroxy-6-(α -ethyl-[p-fluorophenethyl])-2H-pyran-2-one;
 one;
 3-(α -ethyl(5-methyl(furfur-2-yl)))-4-hydroxy-6-(α -ethyl-[p-chlorophenethyl])-2H-pyran-2-one;
 25 3-(α -ethyl(5-methyl(furfur-2-yl)))-4-hydroxy-6-(α -ethyl-[p-bromophenethyl])-2H-pyran-2-one;
 3-(α -ethyl(5-methyl(furfur-2-yl)))-4-hydroxy-6-(α -ethyl-[p-methylphenethyl])-2H-pyran-2-one;
 3-(α -ethyl(5-methyl(furfur-2-yl)))-4-hydroxy-6-(α -ethyl-[p-methoxyphenethyl])-2H-pyran-2-one;
 30 3-(α -ethyl(5-methyl(furfur-2-yl)))-4-hydroxy-6-(α -ethyl-[p-hydroxyphenethyl])-2H-pyran-2-one;
 3-(α -ethyl(5-methyl(furfur-2-yl)))-4-hydroxy-6-(α -ethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-one;
 35 3-(α -ethyl(5-methyl(furfur-2-yl)))-4-hydroxy-6-(α -ethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-one;

- 3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-fluorophenethyl])-2H-pyran-2-one;
- 3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-chlorophenethyl])-2H-pyran-2-one;
- 5 3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-bromophenethyl])-2H-pyran-2-one;
- 3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-methylphenethyl])-2H-pyran-2-one;
- 3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-methoxyphenethyl])-2H-pyran-2-one;
- 10 3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-hydroxyphenethyl])-2H-pyran-2-one;
- 3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-one;
- 15 3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-one;
- 3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(tetrahydrofuran-2-ylmethyl)propyl)-2H-pyran-2-one;
- 3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(tetrahydrofuran-3-ylmethyl)propyl)-2H-pyran-2-one;
- 20 3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(tetrahydrofuran-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
- 3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(tetrahydrofuran-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
- 25 3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(tetrahydropyran-2-ylmethyl)propyl)-2H-pyran-2-one;
- 3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(tetrahydropyran-3-ylmethyl)propyl)-2H-pyran-2-one;
- 3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(tetrahydropyran-4-ylmethyl)propyl)-2H-pyran-2-one;
- 30 3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(tetrahydropyran-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
- 3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(tetrahydropyran-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
- 35 3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(tetrahydropyran-4-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;

- 3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(furan-2-ylmethyl)propyl)-2H-pyran-2-one;
- 3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(furan-3-ylmethyl)propyl)-2H-pyran-2-one;
- 5 3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(thiophen-2-ylmethyl)propyl)-2H-pyran-2-one;
- 3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(thiophen-3-ylmethyl)propyl)-2H-pyran-2-one;
- 3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(furan-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
- 10 2H-pyran-2-one;
- 3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(furan-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
- 3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(thiophen-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
- 15 3-(α -ethyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(thiophen-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
- 3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one;
- 3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -ethyl-[p-fluorophenethyl])-2H-pyran-2-one;
- 20 3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -ethyl-[p-chlorophenethyl])-2H-pyran-2-one;
- 3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -ethyl-[p-bromophenethyl])-2H-pyran-2-one;
- 25 3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -ethyl-[p-methylphenethyl])-2H-pyran-2-one;
- 3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -ethyl-[p-methoxyphenethyl])-2H-pyran-2-one;
- 3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -ethyl-[p-hydroxyphenethyl])-2H-pyran-2-one;
- 30 3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -ethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-one;
- 3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -ethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-one;
- 35 3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-fluorophenethyl])-2H-pyran-2-one;

3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-chlorophenethyl])-2H-pyran-2-one;

3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-bromophenethyl])-2H-pyran-2-one;

3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-methylphenethyl])-2H-pyran-2-one;

3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-methoxyphenethyl])-2H-pyran-2-one;

3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-hydroxyphenethyl])-2H-pyran-2-one;

3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-one;

3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-one;

3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(tetrahydrofuran-2-ylmethyl)propyl)-2H-pyran-2-one;

3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(tetrahydrofuran-3-ylmethyl)propyl)-2H-pyran-2-one;

3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(tetrahydrofuran-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;

3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(tetrahydrofuran-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;

3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(tetrahydropyran-2-ylmethyl)propyl)-2H-pyran-2-one;

3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(tetrahydropyran-3-ylmethyl)propyl)-2H-pyran-2-one;

3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(tetrahydropyran-4-ylmethyl)propyl)-2H-pyran-2-one;

3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(tetrahydropyran-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;

3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(tetrahydropyran-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;

3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(tetrahydropyran-4-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;

3-(α -cyclopropyl(5-methyl(furfur-2-yl)))4-hydroxy-6-(1-(furan-2-ylmethyl)propyl)-2H-pyran-2-one;

- 3-(α -cyclopropyl(5-methyl(furfur-2-yl)))-4-hydroxy-6-(1-(furan-3-ylmethyl)propyl)-2H-pyran-2-one;
- 3-(α -cyclopropyl(5-methyl(furfur-2-yl)))-4-hydroxy-6-(1-(thiophen-2-ylmethyl)propyl)-2H-pyran-2-one;
- 5 3-(α -cyclopropyl(5-methyl(furfur-2-yl)))-4-hydroxy-6-(1-(thiophen-3-ylmethyl)propyl)-2H-pyran-2-one;
- 3-(α -cyclopropyl(5-methyl(furfur-2-yl)))-4-hydroxy-6-(1-(furan-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
- 3-(α -cyclopropyl(5-methyl(furfur-2-yl)))-4-hydroxy-6-(1-(furan-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
- 10 3-(α -cyclopropyl(5-methyl(furfur-2-yl)))-4-hydroxy-6-(1-(thiophen-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
- 3-(α -cyclopropyl(5-methyl(furfur-2-yl)))-4-hydroxy-6-(1-(thiophen-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
- 15 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one;
- 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethyl-[p-fluorophenethyl])-2H-pyran-2-one;
- one;
- 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethyl-[p-chlorophenethyl])-2H-pyran-2-one;
- one;
- 20 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethyl-[p-bromophenethyl])-2H-pyran-2-one;
- one;
- 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethyl-[p-methylphenethyl])-2H-pyran-2-one;
- one;
- 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethyl-[p-methoxyphenethyl])-2H-pyran-2-one;
- 25 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethyl-[p-hydroxyphenethyl])-2H-pyran-2-one;
- 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-one;
- 30 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-one;
- 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-fluorophenethyl])-2H-pyran-2-one;
- 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-chlorophenethyl])-2H-pyran-2-one;
- 35 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-

- bromophenethyl))-2H-pyran-2-one;
- 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-methylphenethyl])-2H-pyran-2-one;
- 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-methoxyphenethyl])-2H-pyran-2-one;
- 5 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-hydroxyphenethyl])-2H-pyran-2-one;
- 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-one;
- 10 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-one;
- 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(tetrahydrofuran-2-ylmethyl)propyl)-2H-pyran-2-one;
- 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(tetrahydrofuran-3-ylmethyl)propyl)-2H-pyran-2-one;
- 15 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(tetrahydrofuran-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
- 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(tetrahydrofuran-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
- 20 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(tetrahydropyran-2-ylmethyl)propyl)-2H-pyran-2-one;
- 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(tetrahydropyran-3-ylmethyl)propyl)-2H-pyran-2-one;
- 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(tetrahydropyran-4-ylmethyl)propyl)-2H-pyran-2-one;
- 25 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(tetrahydropyran-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
- 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(tetrahydropyran-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
- 30 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(tetrahydropyran-4-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
- 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(furan-2-ylmethyl)propyl)-2H-pyran-2-one;
- 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(furan-3-ylmethyl)propyl)-2H-pyran-2-one;
- 35 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(thiophen-2-ylmethyl)propyl)-2H-pyran-

- 2-one;
 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(thiophen-3-ylmethyl)propyl)-2H-pyran-
 2-one;
 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(furan-2-ylmethyl)cyclopropylmethyl)-
 5 2H-pyran-2-one;
 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(furan-3-ylmethyl)cyclopropylmethyl)-
 2H-pyran-2-one;
 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(thiophen-2-
 ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
 10 3-(α -ethyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(thiophen-3-
 ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one;
 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethyl-[p-fluorophenethyl])-2H-
 pyran-2-one;
 15 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethyl-[p-chlorophenethyl])-2H-
 pyran-2-one;
 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethyl-[p-bromophenethyl])-2H-
 pyran-2-one;
 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethyl-[p-methylphenethyl])-2H-
 20 pyran-2-one;
 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethyl-[p-methoxyphenethyl])-
 2H-pyran-2-one;
 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethyl-[p-hydroxyphenethyl])-2H-
 pyran-2-one;
 25 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethyl-[p-
 trifluoromethylphenethyl])-2H-pyran-2-one;
 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -ethyl-[p-
 trifluoromethylphenethyl])-2H-pyran-2-one;
 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-
 30 fluorophenethyl])-2H-pyran-2-one;
 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-
 chlorophenethyl])-2H-pyran-2-one;
 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-
 bromophenethyl])-2H-pyran-2-one;
 35 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-
 methylphenethyl])-2H-pyran-2-one;

- 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-methoxyphenethyl])-2H-pyran-2-one;
- 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-hydroxyphenethyl])-2H-pyran-2-one;
- 5 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-one;
- 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(α -cyclopropylmethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-one;
- 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(tetrahydrofuran-2-ylmethyl)propyl)-2H-pyran-2-one;
- 10 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(tetrahydrofuran-3-ylmethyl)propyl)-2H-pyran-2-one;
- 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(tetrahydrofuran-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
- 15 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(tetrahydrofuran-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
- 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(tetrahydropyran-2-ylmethyl)propyl)-2H-pyran-2-one;
- 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(tetrahydropyran-3-ylmethyl)propyl)-2H-pyran-2-one;
- 20 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(tetrahydropyran-4-ylmethyl)propyl)-2H-pyran-2-one;
- 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(tetrahydropyran-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
- 25 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(tetrahydropyran-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
- 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(tetrahydropyran-4-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
- 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(furan-2-ylmethyl)propyl)-2H-pyran-2-one;
- 30 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(furan-3-ylmethyl)propyl)-2H-pyran-2-one;
- 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(thiophen-2-ylmethyl)propyl)-2H-pyran-2-one;
- 35 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(thiophen-3-ylmethyl)propyl)-2H-pyran-2-one;

- 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(furan-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
- 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(furan-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
- 5 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(thiophen-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
- 3-(α -cyclopropyl(thiophen-2-ylmethyl))-4-hydroxy-6-(1-(thiophen-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
- 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))-4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-
- 10 one;
- 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))-4-hydroxy-6-(α -ethyl-[p-fluorophenethyl])-2H-pyran-2-one;
- 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))-4-hydroxy-6-(α -ethyl-[p-chlorophenethyl])-2H-pyran-2-one;
- 15 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))-4-hydroxy-6-(α -ethyl-[p-bromophenethyl])-2H-pyran-2-one;
- 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))-4-hydroxy-6-(α -ethyl-[p-methylphenethyl])-2H-pyran-2-one;
- 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))-4-hydroxy-6-(α -ethyl-[p-methoxyphenethyl])-2H-pyran-2-one;
- 20 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))-4-hydroxy-6-(α -ethyl-[p-hydroxyphenethyl])-2H-pyran-2-one;
- 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))-4-hydroxy-6-(α -ethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-one;
- 25 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))-4-hydroxy-6-(α -ethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-one;
- 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))-4-hydroxy-6-(α -cyclopropylmethyl-[p-fluorophenethyl])-2H-pyran-2-one;
- 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))-4-hydroxy-6-(α -cyclopropylmethyl-[p-chlorophenethyl])-2H-pyran-2-one;
- 30 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))-4-hydroxy-6-(α -cyclopropylmethyl-[p-bromophenethyl])-2H-pyran-2-one;
- 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))-4-hydroxy-6-(α -cyclopropylmethyl-[p-methylphenethyl])-2H-pyran-2-one;
- 35 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))-4-hydroxy-6-(α -cyclopropylmethyl-[p-methoxyphenethyl])-2H-pyran-2-one;

- 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-hydroxyphenethyl])-2H-pyran-2-one;
- 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-one;
- 5 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-one;
- 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(tetrahydrofuran-2-ylmethyl)propyl)-2H-pyran-2-one;
- 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(tetrahydrofuran-3-ylmethyl)propyl)-2H-pyran-2-one;
- 10 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(tetrahydrofuran-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
- 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(tetrahydrofuran-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
- 15 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(tetrahydropyran-2-ylmethyl)propyl)-2H-pyran-2-one;
- 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(tetrahydropyran-3-ylmethyl)propyl)-2H-pyran-2-one;
- 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(tetrahydropyran-4-ylmethyl)propyl)-2H-pyran-2-one;
- 20 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(tetrahydropyran-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
- 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(tetrahydropyran-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
- 25 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(tetrahydropyran-4-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
- 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(furan-2-ylmethyl)propyl)-2H-pyran-2-one;
- 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(furan-3-ylmethyl)propyl)-2H-pyran-2-one;
- 30 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(thiophen-2-ylmethyl)propyl)-2H-pyran-2-one;
- 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(thiophen-3-ylmethyl)propyl)-2H-pyran-2-one;
- 35 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(furan-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;

- 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(furan-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
- 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(thiophen-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
- 5 3-(α -ethyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(thiophen-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
- 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(α -ethylphenethyl)-2H-pyran-2-one;
- 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(α -ethyl-[p-fluorophenethyl])-2H-pyran-2-one;
- 10 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(α -ethyl-[p-chlorophenethyl])-2H-pyran-2-one;
- 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(α -ethyl-[p-bromophenethyl])-2H-pyran-2-one;
- 15 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(α -ethyl-[p-methylphenethyl])-2H-pyran-2-one;
- 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(α -ethyl-[p-methoxyphenethyl])-2H-pyran-2-one;
- 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(α -ethyl-[p-hydroxyphenethyl])-2H-pyran-2-one;
- 20 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(α -ethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-one;
- 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(α -ethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-one;
- 25 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-fluorophenethyl])-2H-pyran-2-one;
- 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-chlorophenethyl])-2H-pyran-2-one;
- 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-bromophenethyl])-2H-pyran-2-one;
- 30 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-methylphenethyl])-2H-pyran-2-one;
- 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-methoxyphenethyl])-2H-pyran-2-one;
- 35 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-hydroxyphenethyl])-2H-pyran-2-one;

- 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-one;
- 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(α -cyclopropylmethyl-[p-trifluoromethylphenethyl])-2H-pyran-2-one;
- 5 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(tetrahydrofuran-2-ylmethyl)propyl)-2H-pyran-2-one;
- 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(tetrahydrofuran-3-ylmethyl)propyl)-2H-pyran-2-one;
- 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(tetrahydrofuran-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
- 10 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(tetrahydrofuran-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
- 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(tetrahydropyran-2-ylmethyl)propyl)-2H-pyran-2-one;
- 15 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(tetrahydropyran-3-ylmethyl)propyl)-2H-pyran-2-one;
- 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(tetrahydropyran-4-ylmethyl)propyl)-2H-pyran-2-one;
- 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(tetrahydropyran-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
- 20 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(tetrahydropyran-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
- 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(tetrahydropyran-4-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
- 25 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(furan-2-ylmethyl)propyl)-2H-pyran-2-one;
- 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(furan-3-ylmethyl)propyl)-2H-pyran-2-one;
- 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(thiophen-2-ylmethyl)propyl)-2H-pyran-2-one;
- 30 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(thiophen-3-ylmethyl)propyl)-2H-pyran-2-one;
- 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(furan-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;
- 35 3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(furan-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;

3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(thiophen-2-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;

3-(α -cyclopropyl(5-methyl(thiophen-2-ylmethyl)))4-hydroxy-6-(1-(thiophen-3-ylmethyl)cyclopropylmethyl)-2H-pyran-2-one;

5 N-[5-[(α -Cyclopropyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]furfur-2-yl]-phenylsulfonamide;

N-[5-[(α -Cyclopropyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-ylmethyl]-phenylsulfonamide;

10 N-[5-[(α -Cyclopropyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]furfur-2-yl]-p-fluorophenylsulfonamide;

N-[5-[(α -Cyclopropyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-ylmethyl]-p-fluorophenylsulfonamide;

N-[5-[(α -Cyclopropyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]furfur-2-yl]-p-chlorophenylsulfonamide;

15 N-[5-[(α -Cyclopropyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-ylmethyl]-p-chlorophenylsulfonamide;

N-[5-[(α -Cyclopropyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]furfur-2-yl]-3,4-dichlorophenylsulfonamide;

20 N-[5-[(α -Cyclopropyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-ylmethyl]-3,4-dichlorophenylsulfonamide;

N-[5-[(α -Cyclopropyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]furfur-2-yl]-p-cyanophenylsulfonamide;

N-[5-[(α -Cyclopropyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide;

25 N-[5-[(α -Cyclopropyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]furfur-2-yl]-p-trifluoromethylphenylsulfonamide;

N-[5-[(α -Cyclopropyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-ylmethyl]-p-trifluoromethylphenylsulfonamide;

30 N-[5-[(α -Cyclopropyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]furfur-2-yl]-m-fluorophenylsulfonamide;

N-[5-[(α -Cyclopropyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-ylmethyl]-m-fluorophenylsulfonamide;

N-[5-[(α -Cyclopropyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]furfur-2-yl]-m-chlorophenylsulfonamide;

35 N-[5-[(α -Cyclopropyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-ylmethyl]-m-chlorophenylsulfonamide;

-[5-[(α -Cyclopropyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]furfur-2-
 nophenylsulfonamide;
 -[5-[(α -Cyclopropyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-
 yl]-m-cyanophenylsulfonamide;
 -[5-[(α -Cyclopropyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]furfur-2-
 fluoromethylphenylsulfonamide;
 -[5-[(α -Cyclopropyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-
 yl]-m-trifluoromethylphenylsulfonamide;
 -[5-[(α -Cyclopropyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]furfur-2-
 rophenylsulfonamide;
 -[5-[(α -Cyclopropyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-
 yl]-o-fluorophenylsulfonamide;
 -[5-[(α -Cyclopropyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]furfur-2-
 rophenylsulfonamide;
 -[5-[(α -Cyclopropyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-
 yl]-o-chlorophenylsulfonamide;
 -[5-[(α -Cyclopropyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]furfur-2-
 nophenylsulfonamide;
 -[5-[(α -Cyclopropyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-
 yl]-o-cyanophenylsulfonamide;
 -[5-[(α -Cyclopropyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]furfur-2-
 fluoromethylphenylsulfonamide;
 -[5-[(α -Cyclopropyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-
 yl]-o-trifluoromethylphenylsulfonamide;
 -[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]furfur-2-yl]-
 lfonamide;
 -[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-
]-phenylsulfonamide;
 -[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]furfur-2-yl]-p-
 enylsulfonamide;
 -[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-
]-p-fluorophenylsulfonamide;
 -[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]furfur-2-yl]-p-
 enylsulfonamide;
 -[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-
]-p-chlorophenylsulfonamide;

- N-[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]furfur-2-yl]-3,4-dichlorophenylsulfonamide;
- N-[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-ylmethyl]-3,4-dichlorophenylsulfonamide;
- 5 N-[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]furfur-2-yl]-p-cyanophenylsulfonamide;
- N-[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-ylmethyl]-p-cyanophenylsulfonamide;
- N-[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]furfur-2-yl]-p-10 trifluoromethylphenylsulfonamide;
- N-[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-ylmethyl]-p-trifluoromethylphenylsulfonamide;
- N-[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]furfur-2-yl]-m-15 fluorophenylsulfonamide;
- N-[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-ylmethyl]-m-fluorophenylsulfonamide;
- N-[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]furfur-2-yl]-m-20 chlorophenylsulfonamide;
- N-[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-ylmethyl]-m-chlorophenylsulfonamide;
- N-[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]furfur-2-yl]-m-25 cyanophenylsulfonamide;
- N-[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-ylmethyl]-m-cyanophenylsulfonamide;
- N-[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]furfur-2-yl]-m-30 trifluoromethylphenylsulfonamide;
- N-[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-ylmethyl]-m-trifluoromethylphenylsulfonamide;
- N-[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]furfur-2-yl]-o-35 fluorophenylsulfonamide;
- N-[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-ylmethyl]-o-fluorophenylsulfonamide;
- N-[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]furfur-2-yl]-o-chlorophenylsulfonamide;
- N-[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-ylmethyl]-o-chlorophenylsulfonamide;

-308-

N-[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]furfur-2-yl]-o-cyanophenylsulfonamide;

N-[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-ylmethyl]-o-cyanophenylsulfonamide;

5 N-[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]furfur-2-yl]-o-trifluoromethylphenylsulfonamide;

N-[5-[(α -Ethyl- α -(6-(α -ethylphenethyl)-4-hydroxy-2-pyran-3-yl)-methyl]thiophen-2-ylmethyl]-o-trifluoromethylphenylsulfonamide;

10 3-(α [S]-Cyclopropyl(m-fluorobenzyl))-4-hydroxy-6-(α [R]-ethyl- β -tetrahydropyran-4-yl)ethyl-2H-pyran-2-one;

3-(α [S]-Cyclopropyl(m-fluorobenzyl))-4-hydroxy-6-(α [S]-ethyl- β -tetrahydropyran-4-yl)ethyl-2H-pyran-2-one;

3-(α [S]-Cyclopropyl(m-fluorobenzyl))-4-hydroxy-6-(α [R]-ethyl- β -tetrahydropyran-4-yl)ethyl-2H-pyran-2-one;

15 3-(α [S]-Cyclopropyl(m-fluorobenzyl))-4-hydroxy-6-(α [S]-ethyl- β -tetrahydropyran-4-yl)ethyl-2H-pyran-2-one;

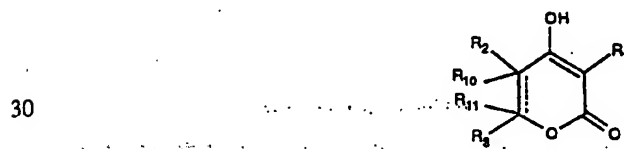
3-(α [R]-Cyclopropyl(m-fluorobenzyl))-4-hydroxy-6-(α [R]-ethyl- β -tetrahydropyran-4-yl)ethyl-2H-pyran-2-one;

20 3-(α [R]-Cyclopropyl(m-fluorobenzyl))-4-hydroxy-6-(α [S]-ethyl- β -tetrahydropyran-4-yl)ethyl-2H-pyran-2-one;

3-(α [R]-Cyclopropyl(m-fluorobenzyl))-4-hydroxy-6-(α [R]-ethyl- β -tetrahydropyran-4-yl)ethyl-2H-pyran-2-one; and

3-(α [R]-Cyclopropyl(m-fluorobenzyl))-4-hydroxy-6-(α [S]-ethyl- β -tetrahydropyran-4-yl)ethyl-2H-pyran-2-one.

25 20. Use of a compound of formula I



to prepare a medicament for inhibiting a retrovirus in a mammalian cell infected with said
35 retrovirus;
wherein R₁ is

-309-

- a) $-(CH_2)_n-CH(R_5)-(CH_2)_m-R_4$,
- b) $-CH(aryl)-CH[C(O)-O-C_1-C_6 \text{ alkyl}]_2$,
- c) $-C(C_3-C_5 \text{ cycloalkyl})-(CH_2)_n-R_4$,
- d) $-C(aryl)=CH-aryl$,
- 5 e) $-CH(R_5)-S-(CH_2)_m-R_4$, or
- f) $-(CH_2)_p-aryl$;

wherein R_2 is

- a) hydrogen,
- b) halo,
- 10 c) $C_1-C_6 \text{ alkyl}-[O-(CH_2)_2]_q-(CH_2)_n$,
- d) $C_1-C_6 \text{ alkyl}$, or
- e) $-(CH_2)_n-CH(R_5)-(CH_2)_m-R_4$;

wherein R_3 is

- a) $C_1-C_{10} \text{ alkyl}$ optionally substituted by zero (0) to five (5) halo,
- 15 b) $C_2-C_{10} \text{ alkenyl}$,
- c) $R_4-(CH_2)_m-CH(R_6)-(CH_2)_n$,
- d) $R_4-(CH_2)_p$,
- e) $R_4-CH=CH$,
- f) $CH_2=CH-(CH_2)_p$,
- 20 g) $R_4(CH_2)_mX_1C(O)(CH_2)_n$,
- h) $R_4(CH_2)_mC(O)X_1(CH_2)_n$,
- i) aryl,
- j) het,
- k) $C_3-C_7 \text{ cycloalkyl}$,
- 25 l) $C_1-C_6 \text{ alkyl}-O-C(O)-(CH_2)_n$,
- m) $C_1-C_6 \text{ alkyl}-[O-(CH_2)_2]_q-(CH_2)_n$,
- n) $R_4-CH(R_6)-CH(R_6)$,
- p) $R_{12}-(CH_2)_m-X_2-(CH_2)_n-(R_7)HC$, or
- q) $R_{15}-(CH_2)_m-X_2-(CH_2)_n-(R_7)HC$;

30 wherein R_4 is

- a) aryl,
- b) het,
- c) $C_3-C_7 \text{ cycloalkyl}$,
- d) $C_2-C_{10} \text{ alkenyl}$,
- 35 e) $C_1-C_6 \text{ alkyl}-[O-(CH_2)_2]_q-(CH_2)_n$,
- f) halo,

-310-

- g) het-O-,
- h) het-C(O)-,
- i) aryl-(CH₂)_n-O-C(O)-, or
- j) trifluoromethyl;

5 wherein R₅ is

- a) C₁-C₁₀ alkyl,
- b) C₂-C₁₀ alkenyl,
- c) C₃-C₇ cycloalkyl,
- d) -(CH₂)_n-aryl,
- 10 e) -(CH₂)_p-het, or
- f) -(CH₂)_n-CH=CH-aryl;

wherein R₆ is

- a) C₁-C₁₀ alkyl,
- b) R₄-C₁-C₅ alkyl,
- 15 c) -(CH₂)_n-C₃-C₇ cycloalkyl,
- d) -(CH₂)_p-CH=CH₂,
- e) -(CH₂)_p-aryl,
- f) -(CH₂)_p-het, or
- g) hydroxy-;

20 wherein X₁ is -NR₇;wherein R₇ is

- a) hydrogen, or
- b) C₁-C₅ alkyl;

wherein aryl is

- 25 a) phenyl substituted by zero (0) to three(3) R₈,
- b) naphthyl substituted by zero (0) to three(3) R₈,
- c) biphenyl substituted by zero (0) to three (3) R₈, or
- d) perhalophenyl;

30 wherein het is a 5- or 6-membered saturated or unsaturated ring containing from one (1) to four (4) heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring, C₃-C₈ cycloalkyl, or another heterocycle; and if chemically feasible, the nitrogen and sulfur atoms may be in the oxidized forms; and substituted by zero (0) to three (3) R₉;

wherein R₈ and R₉ are independently

- 35 a) C₁-C₈ alkyl substituted by zero (0) to three (3) halo,
- b) C₂-C₈ alkenyl,

-311-

- c) hydroxy,
- d) hydroxy-C₁-C₅ alkyl,
- e) -(CH₂)_n-O-C₁-C₅ alkyl substituted by zero (0) to three (3) hydroxy,
- f) -(CH₂)_n-O-C₂-C₇ alkenyl substituted by zero (0) to three (3) hydroxy,
- 5 g) halo,
- h) amino,
- i) amino-C₁-C₅ alkyl,
- j) mono-or di-C₁-C₅ alkylamino,
- k) -C(O)-C₁-C₅ alkyl,
- 10 l) -CHO,
- m) -COOH,
- n) -COOC₁-C₅ alkyl,
- o) -CON(R₇)₂,
- p) C₃-C₇ cycloalkyl,
- 15 q) nitro,
- r) -CN,
- s) -SO₃H,
- t) -SO₂NH₂,
- u) -O[(CH₂)₂-O]_q-CH₃,
- 20 v) -[CH₂-O]_q-C₁-C₃ alkyl,
- w) -(CH₂)_n-NHC(O)-O-(CH₂)_p-R₁₂,
- x) -(CH₂)_n-NHC(O)-O-(CH₂)_p-R₁₅,
- y) -(CH₂)_n-R₁₂,
- z) -SO₂-R₁₂,
- 25 a1) -(CH₂)_n-X₂-(CH₂)_n-R₁₂,
- b1) -(CH₂)_n-X₂-(CH₂)_n-R₁₅,
- c1) -(CH₂)_n-X₂-CH=CH-R₁₂,
- d1) -(CH₂)_n-X₂-CH=CH-R₁₅,
- e1) -(CH₂)_n-X₂-C₁-C₁₀alkyl substituted by zero (0) to three (3) halo,
- 30 f1) -(CH₂)_n-X₂-C₂-C₅ alkenyl,
- g1) -X₂-(CH₂)_p-CH(NH₂)(COOH),
- h1) -NHCONH-SO₂-R₁₂,
- i1) -X₂-(CH₂)_p-NH-C(O)-O-C₁-C₆ alkyl,
- j1) -X₂-CH(X₃)-NH-C(O)-O-C₁-C₆ alkyl,
- 35 k1) -X₂-(CH₂)_p-CH[NH-C(O)-O-(CH₂)_p-R₁₂]-C(O)-O-(CH₂)_p-R₁₂,
- l1) -(CH₂)_n-X₄-N(C₁-C₃ alkyl)₂,

-312-

- m1) $-(CH_2)_n-X_4-NHR_{12}$,
 n1) $-NH-AA-P_1$,
 o1) $-(CH_2)_p-N_3$,
 p1) $-(CH_2)_p-R_{12}$,
 5 q1) $-(CH_2)_p-R_{15}$,
 r1) $-(CH_2)_n-NHC(SCH_3)=CHNO_2$,
 s1) $-(CH_2)_n-NHC(NHR_7)=CHNO_2$,
 t1) $-(CH_2)_n-NHC(SCH_3)=NCN$, or
 u1) $-(CH_2)_n-NHC(NHR_7)=NCN$;

10 wherein X_2 is

- a) $-NH-C(O)-$,
 b) $-NH-SO_2-$,
 c) $-NH-C(O)-NH-$, or
 d) $-SO_2-NH-$;

15 wherein X_3 is

- a) C_1-C_6 alkyl, or
 b) $-(CH_2)_p-R_{15}$;

wherein X_4 is

- a) $-NH-C(O)-$, or
 20 b) $-NH-SO_2-$;

wherein R_{10} is hydrogen;wherein R_{11} is

- a) hydrogen,
 b) C_1-C_6 alkyl,
 25 c) $-(CH_2)_n$ -aryl,
 d) $-(CH_2)_n-C_3-C_7$ cycloalkyl, or
 e) $-(CH_2)_n$ -bet;

or wherein R_{10} and R_{11} taken together form a double bond;or wherein R_3 and R_{11} taken together form

- 30 a) C_3-C_8 cycloalkyl substituted by zero (0) to three (3) hydroxy, $=N-OH$, $=O$
 (oxo), or protected form thereof, or substituted at the α -position by R_{14} ; or
 b) a 5- or 6-membered saturated ring containing one (1) or two (2) oxygen atoms;

wherein R_{12} is

- a) phenyl substituted by zero (0) to three (3) R_{13} , or
 35 b) naphthyl substituted by zero (0) to three (3) R_{13} ;

wherein R_{13} is

-313-

- a) C_1-C_{10} alkyl substituted by zero (0) to three (3) halo,
 b) hydroxy,
 c) hydroxy- C_1-C_5 alkyl,
 d) $-(CH_2)_n-O-C_1-C_5$ alkyl substituted by zero (0) to three (3) hydroxy or halo,
 5 e) $-(CH_2)_n-O-C_2-C_7$ alkenyl substituted by zero (0) to three (3) hydroxy or halo,
 f) halo,
 g) amino,
 h) amino C_1-C_5 alkyl,
 i) mono-or di- C_1-C_5 alkylamino,
 10 j) $-C(O)-C_1-C_5$ alkyl,
 k) $-CHO$,
 l) $-COOH$,
 m) $-CON(R_7)_2$,
 n) $-NHCOC_1-C_3$ alkyl,
 15 o) $-NHOH$,
 p) nitro,
 q) $-CN$,
 r) $-(CH_2)_n$ -phenyl,
 s) $-COOC_1-C_5$ alkyl, or
 20 t) $-SO_2$ -phenyl substituted by zero (0) to three (3) C_1-C_5 alkyl,
 u) $-(CH_2)_n-X_4$ -phenyl, or
 v) $-(CH_2)_n-N=N$ -phenyl substituted by zero (0) or one (1) $-N(C_1-C_3 \text{ alkyl})_2$;

wherein R_{14} is

- a) $-(CH_2)_n$ -aryl,
 25 b) $-C_1-C_6$ alkyl, or
 c) $-(CH_2)_n-C_4-C_7$ cycloalkyl;

wherein R_{15} is a 5- or 6-membered saturated or unsaturated ring containing from one (1) to four (4) heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring, C_3 -

- 30 C_8 cycloalkyl, or another heterocycle; and substituted by zero (0) to three (3) R_{13} ;

wherein AA is an amino acid residue;

wherein P_1 is hydrogen or a nitrogen protecting group;

wherein m and n are independently zero (0) to five (5) inclusive;

wherein p is one (1) to five (5) inclusive;

- 35 wherein q is one (1) to five (5) inclusive; and

pharmaceutically acceptable salts thereof.

-314-

21. The use of claim 20

wherein R_1 is $-\text{CH}(R_5)-R_4$;

wherein R_2 is hydrogen;

wherein R_3 is

- a) $\text{C}_3\text{-C}_8$ alkyl,
- b) $R_4-(\text{CH}_2)_m-\text{CH}(\text{C}_6)-$,
- c) $R_4-(\text{CH}_2)_p-$,
- d) $R_4-\text{CH}=\text{CH}-$,
- e) $\text{CH}_2=\text{CH}-(\text{CH}_2)_p-$,
- f) $R_4-\text{NH}-\text{C}(\text{O})-\text{CH}_2-$,

wherein R_4 is aryl;

wherein R_5 is

- a) $\text{C}_2\text{-C}_5$ alkyl,
- b) $\text{C}_2\text{-C}_5$ alkenyl,
- c) cyclopropyl;

wherein R_6 is

- a) $\text{C}_2\text{-C}_5$ alkyl, or
- b) $R_4\text{-C}_1\text{-C}_2$ alkyl-;

wherein aryl is

- a) phenyl substituted by zero (0) to three (3) R_8 , or
- b) naphthyl substituted by zero (0) to three (3) R_8 ;

wherein R_8 is

- a) halo, or
- b) $\text{C}_1\text{-C}_3$ alkoxy;

wherein R_{10} and R_{11} taken together form a double bond;

wherein m is one (1) to three (3) inclusive;

wherein p is one (1) to three (3) inclusive.

22. The use of claim 21 wherein the compound is selected from the group consisting of:

- 3-(.alpha.-ethylbenzyl)-4-hydroxy-6-phenyl-2H-Pyran-2-one;
- 6-benzyl-3-(.alpha.-ethylbenzyl)-4-hydroxy-2H-Pyran-2-one;
- 3-(.alpha.-ethylbenzyl)-6-phenethyl-4-hydroxy-2H-Pyran-2-one;
- 4-hydroxy-6-phenethyl-3-(.alpha.-propyl-p-bromobenzyl)-2H-Pyran-2-one;
- 6-(p-bromophenethyl)-3-(.alpha.-ethylbenzyl)-4-hydroxy-2H-Pyran-2-one;
- 3-(.alpha.-ethylbenzyl)-6-(o-fluorophenethyl)-4-hydroxy-2H-Pyran-2-one;
- 3-(.alpha.-ethylbenzyl)-4-hydroxy-6-(3-phenylpropyl)-2H-Pyran-2-one;

-315-

3-(.alpha.-ethylbenzyl)-4-hydroxy-6-propyl-2H-Pyran-2-one;
 3-(.alpha.-ethylbenzyl)-4-hydroxy-6-(3-butenyl)-2H-Pyran-2-one;
 3-(.alpha.-ethylbenzyl)-4-hydroxy-6-[[[(phenylamino)carbonyl]methyl]-2H-Pyran-2-one;
 4-hydroxy-6-phenethyl-3-(.alpha.-vinylbenzyl)-2H-Pyran-2-one;
 3-(.alpha.-ethylbenzyl)-6-(.alpha.ethylphenethyl)-4-hydroxy-2H-Pyran-2-one;
 3-(.alpha.-ethylbenzyl)-1-ethylpropyl-4-hydroxy-2H-Pyran-2-one;
 3-(.alpha.-ethylbenzyl)-4-hydroxy-6-(p-methoxystyryl)-2H-Pyran-2-one;
 3-(.alpha.-ethylbenzyl)-4-hydroxy-6-(2-naphth-2-ylethyl)-2H-Pyran-2-one;
 3-(.alpha.-ethylbenzyl)-4-hydroxy-6-(1-ethyl-2-naphth-2-ylethyl)-2H-Pyran-2-one;
 3-(.alpha.-ethylbenzyl)-4-hydroxy-6-(2-naphth-1-ylethyl)-2H-Pyran-2-one;
 3-(.alpha.-ethylbenzyl)-4-hydroxy-6-(1-ethyl-2-naphth-1-ylethyl)-2H-Pyran-2-one;
 3-(.alpha.-cyclopropylbenzyl)-4-hydroxy-6-(3-phenylpropyl)-2H-Pyran-2-one;
 3-(.alpha.-cyclopropylbenzyl)-6-(1-ethyl propyl)-4-hydroxy-2H-Pyran-2-one;
 3-(.alpha.-cyclopropylbenzyl)-6-(.alpha.-benzylphenethyl)-4-hydroxy-2H-Pyran-2-one;
 3-(.alpha.-cyclopropylbenzyl)-4-hydroxy-6-phenethyl-2H-Pyran-2-one;
 3-(.alpha.-cyclopropylbenzyl)-6-(1-propylbutyl)-4-hydroxy-2H-Pyran-2-one;
 3-(.alpha.-cyclopropylbenzyl)-4-hydroxy-6-methyl-2H-Pyran-2-one; and
 4-Hydroxy-6-methyl-3-(3-phenyl-prop-2-enyl)-2H-pyran-2-one.

23. The use of claim 20 wherein the compound is selected from the group consisting of:

Dimethyl 3-[(4-hydroxy-2-oxo-6-phenyl-2H-1-pyran-3-yl)(4-nitrophenyl)-1,3-propandioate;
 Dimethyl 3-[(4-hydroxy-2-oxo-6-phenyl-2H-1-pyran-3-yl)(3-nitrophenyl)-1,3-propandioate;
 6-Ethyl-3-(.alpha.-ethylbenzyl)-6-phenyl-tetrahydropyran-2,4-dione;
 5,6-Dihydro-4-hydroxy-6-cyclohexyl-6-phenyl-3-[1-(3-hydroxyphenyl)propyl]-2H-pyran-2-one;
 4-Hydroxy-1-oxa-3-(1-phenylpropyl)spiro-[5,5]-undec-3-en-2-one, sodium salt;
 6,6-Diethyl-3-(3-phenylpropyl)-tetrahydropyran-2,4-dione;
 Dihydro-6-methyl-6-phenyl-3-(1-phenyl-2-propenyl)-2H-Pyran-2,4(3H)-dione;
 Dihydro-3-[1-(3-hydroxyphenyl)propyl]-6-phenyl-6-propyl-2H-pyran-2,4(3H)-dione;
 5,6-Dihydro-4-hydroxy-6-phenyl-6-propyl-3-(1-phenylpropyl)-2H-pyran-2-one;
 5,6-Dihydro-4-hydroxy-6-phenyl-6-propyl-3-[1-(3-hydroxyphenyl)-propyl]-2H-pyran-2-one;
 12-Hydroxy-11-(1-phenyl-allyl)-1,4,9-trioxa-dispiro[4.2.5.2]pentadec-11-en-10-one;
 12-Hydroxy-11-(1-phenyl-propyl)-1,4,9-trioxa-dispiro[4.2.5.2]pentadec-11-en-10-one;

- 4-Hydroxy-3-(1-phenyl-propyl)-1-oxa-spiro[5.5]undec-3-ene-2,9-dione;
 6,6-Dibenzyl-4-hydroxy-3-(1-phenyl-propyl)-5,6-dihydro-pyran-2-one;
 4-Hydroxy-3-(1-phenyl-allyl)-1,9-dioxo-spiro[5.5]undec-3-en-2-one;
 4,9-Dihydroxy-3-(1-phenyl-propyl)-1-oxa-spiro[5.5]undec-3-en-2-one;
- 5 N-(3-Cyclopropyl-[6-(1-ethyl-phenethyl)-4-hydroxy-2-oxo-5,6-dihydro-2H-pyran-3-yl]-methyl)-phenyl)-3-(*tert*-butyloxycarbonylamino)-propionamide;
 N-(3-{Cyclopropyl-[6-(2-cyclopropyl-1-cyclopropylmethyl-ethyl)-4-hydroxy-2-oxo-5,6-dihydro-2H-pyran-3-yl]-methyl}-phenyl)-3-indol-1-yl-propionamide;
 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(1-(tetrahydro-furan-3-ylmethyl)-propyl)-pyran-2-one;
- 10 6-(1-(5-Chloro-thiophen-2-ylmethyl)-propyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one;
 3-(Cyclopropyl-phenyl-methyl)-6-(1-(3,5-dimethyl-isoxazol-4-ylmethyl)-propyl)-4-hydroxy-pyran-2-one;
- 15 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(1-(tetrahydro-furan-2-ylmethyl)-propyl)-pyran-2-one;
 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(1-thiophen-2-ylmethyl-propyl)-pyran-2-one;
 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(1-tetrahydro-pyran-4-ylmethyl)-propyl)-pyran-2-one;
- 20 3-(Cyclopropyl-phenyl-methyl)-6-(1-furan-2-ylmethyl-propyl)-4-hydroxy-pyran-2-one;
 3-(Cyclopropyl-phenyl-methyl)-6-(1-(1,3)dioxolan-2-ylmethyl-propyl)-4-hydroxy-pyran-2-one;
 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(1-(tetrahydro-pyran-3-ylmethyl)-propyl)-pyran-2-one;
- 25 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(1-(tetrahydro-pyran-2-ylmethyl)-propyl)-pyran-2-one;
 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(1-pyridin-2-ylmethyl-propyl)-pyran-2-one;
 6-(4-Chloro-1-ethyl-butyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one;
 6-(3-Chloro-1-ethyl-propyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one;
- 30 3-(Cyclopropyl-phenyl-methyl)-6-[ethyl-3-(tetrahydro-pyran-2-yloxy)-propyl]-4-hydroxy-pyran-2-one;
 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(1-pyridin-3-ylmethyl-propyl)-pyran-2-one;
 3-(Cyclopropyl-phenyl-methyl)-6-(1-ethyl-3-thiophen-3-yl-propyl)-4-hydroxy-pyran-2-one;
- 35 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-[1-(tetrahydro-pyran-3-ylmethyl)-butyl]-pyran-2-one;

- 5-Bromo-6-(2-cyclopropyl-cyclopropylmethyl-ethyl)-4-hydroxy-3-(1-phenyl-propyl)-pyran-2-one;
3-(1-Benzyl-2-phenyl-ethyl)-6-(2-cyclopropyl-1-cyclopropylmethyl-ethyl)-4-hydroxy-pyran-2-one;
5 6-(2-Cyclopropylmethyl-ethyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one;
6-(1-Allyl-but-3-enyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one; 3-(Cyclopropyl-phenyl-methyl)-6-(1-ethyl-3-(2-methoxy-ethoxy)-propyl)-4-hydroxy-pyran-2-one;
6-(1-Benzyl-3-(2-methoxy-ethoxy)-propyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one;
10 3-(α -Cyclopropyl-*meta*-(benzyloxycarbonylamino)benzyl)-6-(α -ethyl-phenethyl)-4-hydroxy-2H-pyran-2-one;
3-(α -Cyclopropyl-*meta*-(*tert*-butyloxycarbonylamino)benzyl)-6-(α -cyclopropylmethyl-cyclopropylethyl)-4-hydroxy-2H-pyran-2-one;
4-Hydroxy-3-(1-phenyl-propyl)-6-(1-propyl-butyl)-pyran-2-one;
15 4-Hydroxy-3-(1-phenyl-allyl)-6-(1-propyl-butyl)-pyran-2-one;
3-(5-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-oxo-6H-pyran-2-yl)-propionic acid *tert*-butyl ester;
3-(Cyclopropyl-phenyl-methyl)-6-(2-(3,5-dimethyl-isoxazol-4-yl)-ethyl)-4-hydroxy-pyran-2-one;
20 6-(2-(5-*tert*-Butyl-(1,2,4)oxadiazol-3-yl)-ethyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one;
3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(2-phenyl-1-pyridin-2-ylmethyl-ethyl)-pyran-2-one;
3-(Cyclopropyl-phenyl-methyl)-6-(2-(1,3)dioxolan-2-yl-ethyl)-4-hydroxy-pyran-2-one;
25 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(4-morpholin-4-yl-butyl)-pyran-2-one;
3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(2-pyridin-2-yl-ethyl)-pyran-2-one;
3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(2-(2-methyl-thiazol-4-yl)-ethyl)-pyran-2-one;
3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(2-quinolin-2-yl-ethyl)-pyran-2-one;
30 6-(3-Chloro-propyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one;
6-(1-(2-(4-Chloro-phenyl)-thiazol-4-ylmethyl)-propyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one;
3-(Cyclopropyl-phenyl-methyl)-6-(3-(1,3)dioxan-2-yl-1-ethyl-propyl)-4-hydroxy-pyran-2-one;
3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(1-pyridin-4-ylmethyl-propyl)-pyran-2-one;
35 3-(Cyclopropyl-phenyl-methyl)-6-(1-ethyl-3-morpholin-4-yl-3-oxo-propyl)-4-hydroxy-

- pyran-2-one;
 3-(Cyclopropyl-phenyl-methyl)-6-(1-ethyl-4-morpholin-4-yl-butyl)-4-hydroxy-pyran-2-one;
 3-(Cyclopropyl-phenyl-methyl)-6-[1-(2,3-dihydro-benzo[1,4]dioxin-2-ylmethyl)-propyl]-
 5 4-hydroxy-pyran-2-one;
 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-isobutyl-pyran-2-one;
 Cyclopropyl-phenyl-methyl)-6-[1-(5,6-dihydro-2H-pyran-3-ethyl)-propyl]-4-hydroxy-pyran-2-one;
 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-5-(2-(2-methoxy-ethoxy)-ethyl)-6-propyl-
 10 pyran-2-one;
 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(1-isobutyl-3-methyl-butyl)-pyran-2-one;
 3-Dicyclopopylmethyl-4-hydroxy-6-phenethyl-pyran-2-one;
 6-(1-Cyclopropyl-ethyl)-3-dicyclopopylmethyl-4-hydroxy-pyran-2-one;
 6-(1-Cyclopropyl-1-cyclopopylmethyl-ethyl)-3-dicyclopopylmethyl-4-hydroxy-pyran-2-
 15 one;
 6-(1-Cyclohexylmethyl-propyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one;
 6-(1-Benzyl-propyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one;
 6-(2-Cyclopropyl-1-cyclopopylmethyl-ethyl)-4-hydroxy-3-(1-phenyl-propyl)-pyran-2-one;
 6-(1-Benzyl-2-cyclopropyl-ethyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one;
 20 6-(2-Cyclopropyl-ethyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one;
 6-(1-Cyclopopylmethyl-propyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one;
 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(4-phenyl-butyl)-pyran-2-one;
 3-(Cyclohexyl-cyclopopyl-methyl)-6-(2-cyclopropyl-1-cyclopopylmethyl-ethyl)-4-hydroxy-pyran-2-one;
 25 3-(Cyclopropyl-phenyl-methyl)-6-(1-ethyl-4-phenyl-butyl)-4-hydroxy-pyran-2-one;
 6-(3-Cyclohexyl-propyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one;
 6-(3-Cyclohexyl-1-ethyl-propyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one;
 6-(2-Cyclopropyl-ethyl)-4-hydroxy-3-(1-phenyl-propyl)-pyran-2-one;
 6-But-3-enyl-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one;
 30 3-(Cyclopropyl-phenyl-methyl)-6-(1-ethyl-3-phenyl-propyl)-4-hydroxy-pyran-2-one;
 5-Bromo-6-(2-cyclopropyl-ethyl)-4-hydroxy-3-(1-phenyl-propyl)-pyran-2-one;
 6-(1-Benzyl-2-phenyl-ethyl)-4-hydroxy-3-(1-phenyl-propyl)-pyran-2-one;
 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(3-(2-methoxy-ethoxy)-propyl)-pyran-2-one;
 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-5-(2-(2-methoxy-ethoxy)-ethyl)-6-(3-(2-
 35 methoxy-ethoxy)-pyran-2-one;
 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-propyl-pyran-2-one;

- 5-Bromo-4-hydroxy-6-phenylethyl-3-(1-phenyl-propyl)-pyran-2-one;
 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(3-(2-methoxy-ethoxy)-ethoxy)-propyl)-
 pyran-2-one;
 5-Bromo-4-hydroxy-3-(1-phenyl-propyl)-6-propyl-pyran-2-one;
 5 3-(Cyclopropyl-phenyl-methyl)-6-(1-ethyl-propyl)-4-hydroxy-5-(2-(2-methoxy-
 ethoxy)ethyl)-pyran-2-one;
 6-(1-Benzyl-propyl)-5-bromo-4-hydroxy-3-(1-phenyl-propyl)-pyran-2-one;
 6-(2-Cyclopropyl-1-cyclopropylmethyl-ethyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-
 5-(2-(2-methoxy-ethoxy)-ethoxy)-ethyl)-pyran-2-one;
 10 3-(Cyclopropyl-phenyl-methyl)-6-(2-furan-2-yl-2-hydroxy-ethyl)-4-hydroxy-pyran-2;
 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(4,4,4-trifluoro-butyl)-pyran-2-one;
 6-[2-(1-Cyclohexyl-1H-tetrazol-5-yl)-ethyl]-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-2-
 one;
 4-Hydroxy-3-(1-phenyl-propyl)-1-oxa-spiro[5.5]undec-3-ene-2,9-dione monooxime;
 15 5,6-Dihydro-4-hydroxy-6-phenyl-6-(phenylmethyl)-3-(1-phenyl-2-propenyl)-2H-pyran-2-
 one;
 5,6-Dihydro-4-hydroxy-6-phenyl-6-(phenylmethyl)-3-(1-phenylpropyl)-2H-pyran-2-one;
 3-(1,3-Diphenyl-2-propenyl)-5,6-dihydro-4-hydroxy-6-(2-phenylethyl)-6-propyl-, (E)-2H-
 pyran-2-one;
 20 3-(1,3-Diphenyl-2-propyl)-5,6-dihydro-4-hydroxy-6-(2-phenylethyl)-6-propyl-, (E)-2H-
 pyran-2-one;
 3-(1,3-Diphenyl-2-propenyl)-5,6-dihydro-4-hydroxy-6-phenyl-6-(phenylmethyl)-2H-
 pyran-2-one;
 3-(1,2-Diphenylethenyl)-5,6-dihydro-4-hydroxy-6-(2-phenylethyl)-6-propyl-, (E)-2H-
 25 pyran-2-one;
 5,6-Dihydro-4-hydroxy-6-(2-phenylethyl)-3-(1-phenyl-2-propenyl)-6-propyl-2H-pyran-2-
 one;
 5,6-Dihydro-4-hydroxy-6-(2-phenylethyl)-3-(1-phenylpropyl)-6-propyl-2H-pyran-2-one;
 3-(1,3-Diphenyl-2-propenyl)-5,6-dihydro-4-hydroxy-6-(phenylmethyl)-6-propyl-2H-
 30 pyran-2-one;
 3-(1,3-Diphenylpropyl)-5,6-dihydro-4-hydroxy-6-(phenylmethyl)-6-propyl-2H-pyran-2-
 one;
 4-Hydroxy-3-(1-phenylallyl)-1-oxa-spiro[5.6]-dodec-3-en-2-one;
 4-Hydroxy-3-(1-phenylallyl)-1-oxa-spiro[5.4]-dec-3-en-2-one;
 35 7-Benzyl-4-hydroxy-3-(1-phenylallyl)-1-oxa-spiro[5.5]undec-3-en-2-one;
 4-Hydroxy-3-(1-phenylpropyl)-1-oxa-spiro[5.4]-dec-3-en-2-one;

- 4-Hydroxy-3-(1-phenyl-2-propenyl)-1-oxaspiro[5.7]tridec-3-en-2-one;
 4-Hydroxy-3-(1-phenylpropyl)-1-oxaspiro[5.7]tridec-3-en-2-one;
 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(α -ethyl- β -hydroxyphenethyl)-2H-pyran-2-one;
 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(β -hydroxy-p-methylphenethyl)-2H-pyran-2-one;
 5 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(β -hydroxy-p-fluorophenethyl)-2H-pyran-2-one;
 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(β -hydroxy-p-chlorophenethyl)-2H-pyran-2-one;
 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(β -hydroxy-m-chlorophenethyl)-2H-pyran-2-one;
 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(β -hydroxy-o-chlorophenethyl)-2H-pyran-2-one;
 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(2-(furan-3-yl)-2-hydroxyethyl)-2H-pyran-2-one;
 10 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(2-(thiophen-3-yl)-2-hydroxyethyl)-2H-pyran-2-one;
 one;
 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(α -ethyl-p-fluorophenethyl)-2H-pyran-2-one;
 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(α -ethyl-p-chlorophenethyl)-2H-pyran-2-one;
 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(α -ethyl-m-chlorophenethyl)-2H-pyran-2-one;
 15 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(α -ethyl-o-chlorophenethyl)-2H-pyran-2-one;
 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(α -ethyl-p-bromophenethyl)-2H-pyran-2-one;
 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(α -ethyl-m-bromophenethyl)-2H-pyran-2-one;
 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(α -ethyl-p-trifluoromethylphenethyl)-2H-pyran-2-one;
 one;
 20 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(α -ethyl-m-trifluoromethylphenethyl)-2H-pyran-2-one;
 one;
 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(α -ethyl-o-trifluoromethylphenethyl)-2H-pyran-2-one;
 one;
 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(α -ethyl-p-methoxyphenethyl)-2H-pyran-2-one;
 25 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(α -ethyl-m-methoxyphenethyl)-2H-pyran-2-one;
 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(p-fluorophenethyl)-2H-pyran-2-one;
 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(p-chlorophenethyl)-2H-pyran-2-one;
 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(p-bromophenethyl)-2H-pyran-2-one;
 3-(Cyclopropylphenylmethyl)-6-[1-ethyl-3-(4-morpholinyl)propyl]-4-hydroxy-2H-pyran-2-one;
 30 2-one;
 3-(Cyclopropylphenylmethyl)- β -ethyl-4-hydroxy-2-oxo-, phenylmethyl ester 2H-pyran-6-propanoic acid;
 3-(Cyclopropylphenylmethyl)-4-hydroxy-6-[2-methyl-1-(phenylmethyl)propyl]-2H-pyran-2-one;
 2-one;
 35 3-(Cyclopropylphenylmethyl)-4-hydroxy-6-[2-methyl-1-[(tetrahydro-2H-pyran-3-yl)methyl]propyl]-2H-pyran-2-one;

- 4-Hydroxy-3-(1-phenylpropyl)-6-[1-[(tetrahydro-2H-pyran-3-yl)methyl]propyl]-2H-pyran-2-one;
- 3-(Cyclopropylphenylmethyl)-6-(1-ethyl-4,4,4-trifluorobutyl)-4-hydroxy-2H-pyran-2-one;
- 3-[2-[3-(Cyclopropylphenylmethyl)-4-hydroxy-2-oxo-2H-pyran-6-yl]butyl]-1-[(4-methylphenyl)sulfonyl]-piperidine;
- 2-[2-[3-(Cyclopropylphenylmethyl)-4-hydroxy-2-oxo-2H-pyran-6-yl]butyl]-1-[(4-methylphenyl)sulfonyl]-pyrrolidine;
- 3-(Cyclopropylphenylmethyl)-4-hydroxy-6-(3,3,3-trifluoropropyl)-2H-pyran-2-one;
- 2-[2-[3-(Cyclopropylphenylmethyl)-4-hydroxy-2-oxo-2H-pyran-6-yl]butyl]-1-[(4-methylphenyl)sulfonyl]-piperidine;
- 4-[2-[3-(Cyclopropylphenylmethyl)-4-hydroxy-2-oxo-2H-pyran-6-yl]butyl]-1-[(4-methylphenyl)sulfonyl]-piperidine;
- 4-[2-[3-(Cyclopropylphenylmethyl)-4-hydroxy-2-oxo-2H-pyran-6-yl]butyl]-1-(phenylmethyl)-2-pyrrolidinone;
- 6-(Cyclopentylmethyl)-3-(cyclopropylphenylmethyl)-4-hydroxy-2H-pyran-2-one;
- 3-(Cyclopropylphenylmethyl)-4-hydroxy-6-[(tetrahydro-2H-pyran-4-yl)methyl]-2H-pyran-2-one;
- 3-(Cyclopropylphenylmethyl)-6-(3-fluoropropyl)-4-hydroxy-2H-pyran-2-one;
- 4-Hydroxy-3-(1-phenylcyclobutyl)-6-[1-(phenylmethyl)propyl]-2H-pyran-2-one;
- 3-(α -Ethylbenzyl)-6-(α -ethylbenzyl)-4-hydroxy-2H-pyran-2-one;
- 3-(α -Cyclopropyl-*meta*-(phenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 3-(α -Cyclopropyl-*meta*-(propylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 3-(α -Cyclopropyl-*meta*-((E)-2-phenylethenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 3-(α -Cyclopropyl-*meta*-(4-bromophenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 3-(α -Cyclopropyl-*meta*-(2,5-dichlorophenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 3-(α -Cyclopropyl-*meta*-(4-*tert*-butylphenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 3-(α -Cyclopropyl-*meta*-(4-cyanophenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 3-(α -Cyclopropyl-*meta*-(4-methoxyphenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;

- 6-Butyl-5,6-dihydro-3-(1,3-diphenyl-2-propenyl)-4-hydroxy-6-phenylmethyl-2H-pyran-2-one;
- 6-Butyl-5,6-dihydro-3-(1,3-diphenylpropyl)-4-hydroxy-6-phenylmethyl-2H-pyran-2-one;
- 6-Butyl-5,6-dihydro-4-hydroxy-6-phenylmethyl-3-(1-phenyl-2-propenyl)-2H-pyran-2-one;
- 5 6-Butyl-5,6-dihydro-4-hydroxy-6-phenylmethyl-3-(1-phenylpropyl)-2H-pyran-2-one;
- 3-(α -Cyclopropyl-[5-(methoxymethoxy-methyl)-thiophen-2-yl]-methyl)-5,6-dihydro-4-hydroxy-6-(2-methylpropyl)-6-(2-phenylethyl)-2H-pyran-2-one;
- 5,6-Dihydro-4-hydroxy-6-(2-methylpropyl)-6-(2-phenylethyl)-3-(1-phenyl-2-propenyl)-2H-pyran-2-one;
- 10 5,6-dihydro-4-hydroxy-6-(2-methylpropyl)-6-(2-phenylethyl)-3-(1-phenylpropyl)-2H-pyran-2-one;
- 5,6-Dihydro-3-diphenylmethyl-4-hydroxy-6,6-di-(2-phenylethyl)-2H-pyran-2-one;
- 5,6-Dihydro-4-hydroxy-6,6-di-(2-phenylethyl)-3-(1,3-diphenyl-2-propenyl)-2H-pyran-2-one;
- one;
- 15 5,6-Dihydro-4-hydroxy-6,6-di-(2-phenylethyl)-3-(1,3-diphenylpropyl)-2H-pyran-2-one;
- 5,6-Dihydro-4-hydroxy-3-(1,3-diphenyl-2-propenyl)-6-(3-phenylpropyl)-6-propyl-2H-pyran-2-one;
- 5,6-Dihydro-4-hydroxy-3-(1,3-diphenylpropyl)-6-(3-phenylpropyl)-6-propyl-2H-pyran-2-one;
- one;
- 20 3-(α -Cyclopropyl-[5-(methoxymethoxy-methyl)-thiophen-2-yl]-methyl)-5,6-dihydro-4-hydroxy-6-(2-phenylethyl)-6-propyl-2H-pyran-2-one;
- 3-(α -Cyclopropyl-[5-(methoxymethoxy-methyl)-thiophen-2-yl]-methyl)-5,6-dihydro-4-hydroxy-6-(3-phenylpropyl)-6-propyl-2H-pyran-2-one;
- 5,6-Dihydro-3-diphenylmethyl-4-hydroxy-6-(3-phenylpropyl)-6-propyl-2H-pyran-2-one;
- 25 3-Diphenylmethyl-5,6-dihydro-4-hydroxy-6-(2-methylpropyl)-6-(2-phenylethyl)-2H-pyran-2-one;
- 3-(1,3-Diphenyl-2-propenyl)-5,6-dihydro-4-hydroxy-6-(2-methylpropyl)-6-(2-phenylethyl)-2H-pyran-2-one;
- 3-(1,3-Diphenyl-2-propyl)-5,6-dihydro-4-hydroxy-6-(2-methylpropyl)-6-(2-phenylethyl)-2H-pyran-2-one;
- 30 2H-pyran-2-one;
- 3-(α -Cyclopropyl-*meta*-[(phenylaminocarbonyl)amino]benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 3-(α -Cyclopropyl-*meta*-[(4-methoxyphenylaminocarbonyl)amino]benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 35 3-(α -Cyclopropyl-*meta*-[(benzylaminocarbonyl)amino]benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;

3-(α -Cyclopropyl-*meta*-[(4-bromophenylaminocarbonyl)amino]benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;

3-(α -Cyclopropyl-*meta*-[(phenylsulfonylaminocarbonyl)amino]benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;

5 3-(α -Cyclopropyl-*meta*-(N- α -*tert*-butyloxycarbonyl-N-im-p-toluenesulfonyl-L-histidylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;

3-(α -Cyclopropyl-*meta*-(*tert*-butyloxycarbonyl-L-alanyl-amino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;

10 3-(α -Cyclopropyl-*meta*-(4-bromophenylbenzoylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;

3-(α -Cyclopropyl-*meta*-(N- α -*tert*-butyloxycarbonyl-L-histidylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;

3-(α -Cyclopropyl-*meta*-(N-benzyloxycarbonyl-O- α -benzyl-L-glutamylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;

15 3-(α -Cyclopropyl-*meta*-(4-cyanophenylbenzoylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;

3-(α -Cyclopropyl-*meta*-(L-glutamylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;

20 3-(α -Cyclopropyl-*meta*-(3-(1-indolyl)propanoylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;

3-(α -Cyclopropyl-*meta*-(2-pyridylacetyl-amino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;

3-(α -Cyclopropylbenzyl)-6-[1-cyclopropylmethyl-2-(tetrahydropyran-3-yl)ethyl]-4-hydroxy-2H-pyran-2-one;

25 3-(α -Cyclopropyl-*meta*-(3-pyridylacetyl-amino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;

3-(α -Cyclopropyl-*meta*-(4-pyridylacetyl-amino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;

30 3-(α -Cyclopropyl-*meta*-(4-chlorophenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;

3-(α -Cyclopropyl-*meta*-(8-quinolinesulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;

3-(α -Cyclopropyl-*meta*-(ethylsulfonylamino)benzyl)-6-[1-cyclopropylmethyl-2-(tetrahydropyran-3-yl)ethyl]-4-hydroxy-2H-pyran-2-one;

35 3-(α -Cyclopropyl-*meta*-(4-methylphenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-

hydroxy-2H-pyran-2-one;

3-(α -Cyclopropyl-*meta*-(4-methylphenylsulfonylamino)benzyl-6-[1-cyclopropylmethyl-2-(tetrahydropyran-3-yl)ethyl]-4-hydroxy-2H-pyran-2-one;

3-(α -Cyclopropyl-*meta*-(ethylsulfonylamino)benzyl-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;

(3S,6R) 3-(α -ethylbenzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;

(3S,6S) 3-(α -ethylbenzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;

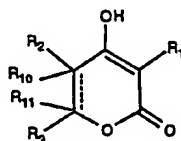
Sodium (3S,6R) 3-(α -ethylbenzyl)-6-(α -ethylphenethyl)-2H-pyran-2-one 4-oxide;

(3R,6R) 3-(α -ethylbenzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one; and

(3R,6S) 3-(α -ethylbenzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one.

24. Use of a compound of formula I

15



I

to prepare a medicament for preventing or treating benign prostatic hypertrophy or hyperplasia, prostatic cancer, alopecia, hirsutism, acne vulgaris and seborrhea in a mammal in need of such prevention or treatment;

wherein R_1 is

- a) $-(CH_2)_n-CH(R_2)-(CH_2)_m-R_4$,
- b) $-CH(aryl)-CH[C(O)-O-C_1-C_6 \text{ alkyl}]_2$,
- c) $-C(C_3-C_5 \text{ cycloalkyl})-(CH_2)_n-R_4$,
- d) $-C(aryl)=CH-aryl$,
- e) $-CH(R_2)-S-(CH_2)_m-R_4$, or
- f) $-(CH_2)_p-aryl$;

wherein R_2 is

- a) hydrogen,
- b) halo,
- c) $C_1-C_6 \text{ alkyl}-[O-(CH_2)_2]_q-(CH_2)_n$,
- d) $C_1-C_6 \text{ alkyl}$, or
- e) $-(CH_2)_n-CH(R_2)-(CH_2)_m-R_4$;

wherein R_3 is

- a) $C_1-C_{10} \text{ alkyl}$ optionally substituted by zero (0) to five (5) halo.

-325-

- b) C_2-C_{10} alkenyl,
 c) $R_4-(CH_2)_m-CH(R_6)-(CH_2)_n$,
 d) $R_4-(CH_2)_p$,
 e) $R_4-CH=CH$,
 5 f) $CH_2=CH-(CH_2)_p$,
 g) $R_4(CH_2)_mX_1C(O)(CH_2)_n$,
 h) $R_4(CH_2)_mC(O)X_1(CH_2)_n$,
 i) aryl,
 j) het,
 10 k) C_3-C_7 cycloalkyl,
 l) C_1-C_6 alkyl-O-C(O)-(CH₂)_n,
 m) C_1-C_6 alkyl-[O-(CH₂)₂]_q-(CH₂)_n,
 n) $R_4-CH(R_6)-CH(R_6)$,
 p) $R_{12}-(CH_2)_m-X_2-(CH_2)_n-(R_7)HC$, or
 15 q) $R_{15}-(CH_2)_m-X_2-(CH_2)_n-(R_7)HC$;

wherein R_4 is

- a) aryl,
 b) het,
 c) C_3-C_7 cycloalkyl,
 20 d) C_2-C_{10} alkenyl,
 e) C_1-C_6 alkyl-[O-(CH₂)₂]_q-(CH₂)_n,
 f) halo,
 g) het-O-,
 h) het-C(O)-,
 25 i) aryl-(CH₂)_n-O-C(O)-, or
 j) trifluoromethyl;

wherein R_5 is

- a) C_1-C_{10} alkyl,
 b) C_2-C_{10} alkenyl,
 30 c) C_3-C_7 cycloalkyl,
 d) $-(CH_2)_n$ -aryl,
 e) $-(CH_2)_p$ -het, or
 f) $-(CH_2)_n-CH=CH$ -aryl;

wherein R_6 is

- 35 a) C_1-C_{10} alkyl,
 b) $R_4-C_1-C_5$ alkyl,

-326-

- c) $-(CH_2)_n-C_3-C_7$ cycloalkyl,
 - d) $-(CH_2)_p-CH=CH_2$,
 - e) $-(CH_2)_p$ -aryl,
 - f) $-(CH_2)_p$ -het, or
 - 5 g) hydroxy-;
- wherein X_1 is $-NR_7$;
- wherein R_7 is
- a) hydrogen, or
 - b) C_1-C_5 alkyl;
- 10 wherein aryl is
- a) phenyl substituted by zero (0) to three (3) R_8 ,
 - b) naphthyl substituted by zero (0) to three (3) R_8 ,
 - c) biphenyl substituted by zero (0) to three (3) R_8 , or
 - d) perhalophenyl;
- 15 wherein het is a 5- or 6-membered saturated or unsaturated ring containing from one (1) to four (4) heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring, C_3-C_8 cycloalkyl, or another heterocycle; and if chemically feasible, the nitrogen and sulfur atoms may be in the oxidized forms; and substituted by zero (0) to three (3) R_9 ;
- 20 wherein R_8 and R_9 are independently
- a) C_1-C_8 alkyl substituted by zero (0) to three (3) halo,
 - b) C_2-C_8 alkenyl,
 - c) hydroxy,
 - d) hydroxy- C_1-C_5 alkyl,
 - 25 e) $-(CH_2)_n-O-C_1-C_5$ alkyl substituted by zero (0) to three (3) hydroxy,
 - f) $-(CH_2)_n-O-C_2-C_7$ alkenyl substituted by zero (0) to three (3) hydroxy,
 - g) halo,
 - h) amino,
 - i) amino- C_1-C_5 alkyl,
 - 30 j) mono-or di- C_1-C_5 alkylamino,
 - k) $-C(O)-C_1-C_5$ alkyl,
 - l) $-CHO$,
 - m) $-COOH$,
 - n) $-COOC_1-C_5$ alkyl,
 - 35 o) $-CON(R_7)_2$,
 - p) C_3-C_7 cycloalkyl,

-327-

- q) nitro,
 r) -CN,
 s) -SO₃H,
 t) -SO₂NH₂,
 5 u) -O[(CH₂)₂-O]_q-CH₃,
 v) -(CH₂-O)_q-C₁-C₃ alkyl,
 w) -(CH₂)_n-NHC(O)-O-(CH₂)_p-R₁₂,
 x) -(CH₂)_n-NHC(O)-O-(CH₂)_p-R₁₅,
 y) -(CH₂)_n-R₁₂,
 10 z) -SO₂-R₁₂,
 a1) -(CH₂)_n-X₂-(CH₂)_n-R₁₂,
 b1) -(CH₂)_n-X₂-(CH₂)_n-R₁₅,
 c1) -(CH₂)_n-X₂-CH=CH-R₁₂,
 d1) -(CH₂)_n-X₂-CH=CH-R₁₅,
 15 e1) -(CH₂)_n-X₂-C₁-C₁₀alkyl substituted by zero (0) to three (3) halo,
 f1) -(CH₂)_n-X₂-C₂-C₅ alkenyl,
 g1) -X₂-(CH₂)_p-CH(NH₂)(COOH),
 h1) -NHCONH-SO₂-R₁₂,
 i1) -X₂-(CH₂)_p-NH-C(O)-O-C₁-C₆ alkyl,
 20 j1) -X₂-CH(X₃)-NH-C(O)-O-C₁-C₆ alkyl,
 k1) -X₂-(CH₂)_p-CH[NH-C(O)-O-(CH₂)_p-R₁₂]-C(O)-O-(CH₂)_p-R₁₂,
 l1) -(CH₂)_n-X₄-N(C₁-C₃ alkyl)₂,
 m1) -(CH₂)_n-X₄-NHR₁₂,
 n1) -NH-AA-P₁,
 25 o1) -(CH₂)_p-N₃,
 p1) -(CH₂)_p-R₁₂,
 q1) -(CH₂)_p-R₁₅,
 r1) -(CH₂)_n-NHC(SCH₃)=CHNO₂,
 s1) -(CH₂)_n-NHC(NHR₇)=CHNO₂,
 30 t1) -(CH₂)_n-NHC(SCH₃)=NCN, or
 u1) -(CH₂)_n-NHC(NHR₇)=NCN;

wherein X₂ is

- a) -NH-C(O)-,
 b) -NH-SO₂-,
 35 c) -NH-C(O)-NH-, or
 d) -SO₂-NH-;

herein X_3 is

- a) C_1-C_6 alkyl, or
- b) $-(CH_2)_p-R_{15}$;

herein X_4 is

- a) $-NH-C(O)-$, or
- b) $-NH-SO_2-$;

herein R_{10} is hydrogen;

herein R_{11} is

- a) hydrogen,
- b) C_1-C_6 alkyl,
- c) $-(CH_2)_n$ -aryl,
- d) $-(CH_2)_n-C_3-C_7$ cycloalkyl, or
- e) $-(CH_2)_n$ -het;

wherein R_{10} and R_{11} taken together form a double bond;

wherein R_3 and R_{11} taken together form

- a) C_3-C_8 cycloalkyl substituted by zero (0) to three (3) hydroxy, $=N-OH$, $=O$ (oxo), or protected form thereof, or substituted at the α -position by R_{14} ; or
- b) a 5- or 6-membered saturated ring containing one (1) or two (2) oxygen atoms;

herein R_{12} is

- a) phenyl substituted by zero (0) to three (3) R_{13} , or
- b) naphthyl substituted by zero (0) to three (3) R_{13} ;

herein R_{13} is

- a) C_1-C_{10} alkyl substituted by zero (0) to three (3) halo,
- b) hydroxy,
- c) hydroxy- C_1-C_5 alkyl,
- d) $-(CH_2)_n-O-C_1-C_5$ alkyl substituted by zero (0) to three (3) hydroxy or halo,
- e) $-(CH_2)_n-O-C_2-C_7$ alkenyl substituted by zero (0) to three (3) hydroxy or halo,
- f) halo,
- g) amino,
- h) amino C_1-C_5 alkyl,
- i) mono- or di- C_1-C_5 alkylamino,
- j) $-C(O)-C_1-C_5$ alkyl,
- k) $-CHO$,
- l) $-COOH$,
- m) $-CON(R_7)_2$,
- n) $-NHCOC_1-C_3$ alkyl,

-329-

- o) -NHOH,
 p) nitro,
 q) -CN,
 r) $-(CH_2)_n$ -phenyl,
 5 s) $-COOC_1-C_5$ alkyl, or
 t) $-SO_2$ -phenyl substituted by zero (0) to three (3) C_1-C_5 alkyl,
 u) $-(CH_2)_n-X_4$ -phenyl, or
 v) $-(CH_2)_n-N=N$ -phenyl substituted by zero (0) or one (1) $-N(C_1-C_3 \text{ alkyl})_2$;

wherein R_{14} is

- 10 a) $-(CH_2)_n$ -aryl,
 b) $-C_1-C_6$ alkyl, or
 c) $-(CH_2)_n-C_4-C_7$ cycloalkyl;

wherein R_{15} is a 5- or 6-membered saturated or unsaturated ring containing from one (1) to four (4) heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur; and including
 15 any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring, C_3-C_8 cycloalkyl, or another heterocycle; and substituted by zero (0) to three (3) R_{13} ;

wherein AA is an amino acid residue;

wherein P_1 is hydrogen or a nitrogen protecting group;

wherein m and n are independently zero (0) to five (5) inclusive;

20 wherein p is one (1) to five (5) inclusive;

wherein q is one (1) to five (5) inclusive; and

pharmaceutically acceptable salts thereof.

25 25. The use of claim 24, wherein the size of the prostate in a male mammal is reduced or maintained.

26. The use of claim 25

wherein R_1 is $-(CH_2)_n-CH(R_3)-(CH_2)_m-R_4$;wherein R_2 is hydrogen;30 wherein R_3 is

- a) $R_4-(CH_2)_m-CH(R_6)-(CH_2)_n$ -, or
 b) $R_4-(CH_2)_p$ -;

wherein R_4 is

- a) phenyl, or
 35 b) tetrahydropyranyl;

wherein R_5 is

-330-

- a) propyl, or
- b) cyclopropyl;

wherein R_6 is ethyl;

wherein m is zero (0) or one (1);

5 wherein n is zero (0);

wherein p is two (2);

wherein R_{10} and R_{11} taken together form a double bond.

27. The use of claim 24 wherein the compound is selected from the group consisting of:
- 10 3-(.alpha.-ethylbenzyl)-4-hydroxy-6-phenyl-2H-Pyran-2-one;
 - 6-benzyl-3-(.alpha.-ethylbenzyl)-4-hydroxy-2H-Pyran-2-one;
 - 3-(.alpha.-ethylbenzyl)-6-phenethyl-4-hydroxy-2H-Pyran-2-one;
 - 4-hydroxy-6-phenethyl-3-(.alpha.-propyl-p-bromobenzyl)-2H-Pyran-2-one;
 - 6-(p-bromophenethyl)-3-(.alpha.-ethylbenzyl)-4-hydroxy-2H-Pyran-2-one;
 - 15 3-(.alpha.-ethylbenzyl)-6-(o-fluorophenethyl)-4-hydroxy-2H-Pyran-2-one;
 - 3-(.alpha.-ethylbenzyl)-4-hydroxy-6-(3-phenylpropyl)-2H-Pyran-2-one;
 - 3-(.alpha.-ethylbenzyl)-4-hydroxy-6-propyl-2H-Pyran-2-one;
 - 3-(.alpha.-ethylbenzyl)-4-hydroxy-6-(3-butenyl)-2H-Pyran-2-one;
 - 3-(.alpha.-ethylbenzyl)-4-hydroxy-6-[(phenylamino)carbonyl]methyl)-2H-Pyran-2-one;
 - 20 4-hydroxy-6-phenethyl-3-(.alpha.-vinylbenzyl)-2H-Pyran-2-one;
 - 3-(.alpha.-ethylbenzyl)-6-(.alpha.-ethylphenethyl)-4-hydroxy-2H-Pyran-2-one;
 - 3-(.alpha.-ethylbenzyl)-1-ethylpropyl-4-hydroxy-2H-Pyran-2-one;
 - 3-(.alpha.-ethylbenzyl)-4-hydroxy-6-(p-methoxystyryl)-2H-Pyran-2-one;
 - 3-(.alpha.-ethylbenzyl)-4-hydroxy-6-(2-naphth-2-ylethyl)-2H-Pyran-2-one;
 - 25 3-(.alpha.-ethylbenzyl)-4-hydroxy-6-(1-ethyl-2-naphth-2-ylethyl)-2H-Pyran-2-one;
 - 3-(.alpha.-ethylbenzyl)-4-hydroxy-6-(2-naphth-1-ylethyl)-2H-Pyran-2-one;
 - 3-(.alpha.-ethylbenzyl)-4-hydroxy-6-(1-ethyl-2-naphth-1-ylethyl)-2H-Pyran-2-one;
 - 3-(.alpha.-cyclopropylbenzyl)-4-hydroxy-6-(3-phenylpropyl)-2H-Pyran-2-one;
 - 3-(.alpha.-cyclopropylbenzyl)-6-(1-ethyl propyl)-4-hydroxy-2H-Pyran-2-one;
 - 30 3-(.alpha.-cyclopropylbenzyl)-6-(.alpha.-benzylphenethyl)-4-hydroxy-2H-Pyran-2-one;
 - 3-(.alpha.-cyclopropylbenzyl)-4-hydroxy-6-phenethyl-2H-Pyran-2-one;
 - 3-(.alpha.-cyclopropylbenzyl)-6-(1-propylbutyl)-4-hydroxy-2H-Pyran-2-one;
 - 3-(.alpha.-cyclopropylbenzyl)-4-hydroxy-6-methyl-2H-Pyran-2-one;
 - 4-Hydroxy-6-methyl-3-(3-phenyl-prop-2-enyl)-2H-pyran-2-one;
 - 35 Dimethyl 3-[(4-hydroxy-2-oxo-6-phenyl-2H-1-pyran-3-yl)(4-nitrophenyl)-1,3-propandioate;

- Dimethyl 3-[(4-hydroxy-2-oxo-6-phenyl-2H-1-pyran-3-yl)(3-nitrophenyl)-1,3-propandioate;
- 6-Ethyl-3-(α -ethylbenzyl)-6-phenyl-tetrahydropyran-2,4-dione;
- 5,6-Dihydro-4-hydroxy-6-cyclohexyl-6-phenyl-3-[1-(3-hydroxyphenyl)propyl]-2H-pyran-2-one;
- 4-hydroxy-1-oxa-3-(1-phenylpropyl)spiro[5.5]undec-3-en-2-one, sodium salt;
- 6,6-Diethyl-3-(3-phenylpropyl)-tetrahydropyran-2,4-dione;
- Dihydro-6-methyl-6-phenyl-3-(1-phenyl-2-propenyl)-2H-Pyran-2,4(3H)-dione;
- Dihydro-3-(1-(3-hydroxyphenyl)propyl)-6-phenyl-6-propyl-2H-pyran-2,4(3H)-dione;
- 5,6-Dihydro-4-hydroxy-6-phenyl-6-propyl-3-(1-phenylpropyl)-2H-pyran-2-one;
- 5,6-Dihydro-4-hydroxy-6-phenyl-6-propyl-3-[1-(3-hydroxyphenyl)propyl]-2H-pyran-2-one;
- 12-Hydroxy-11-(1-phenyl-allyl)-1,4,9-trioxa-dispiro[4.2.5.2]pentadec-11-en-10-one;
- 12-Hydroxy-11-(1-phenyl-propyl)-1,4,9-trioxa-dispiro[4.2.5.2]pentadec-11-en-10-one;
- 4-Hydroxy-3-(1-phenyl-propyl)-1-oxa-spiro[5.5]undec-3-ene-2,9-dione;
- 6,6-Dibenzyl-4-hydroxy-3-(1-phenyl-propyl)-5,6-dihydro-pyran-2-one;
- 4-Hydroxy-3-(1-phenyl-allyl)-1,9-dioxo-spiro[5.5]undec-3-en-2-one;
- 4,9-Dihydroxy-3-(1-phenyl-propyl)-1-oxa-spiro[5.5]undec-3-en-2-one;
- N-(3-Cyclopropyl-[6-(1-ethyl-phenethyl)-4-hydroxy-2-oxo-5,6-dihydro-2H-pyran-3-yl]-methyl)-phenyl)-3-(*tert*-butyloxycarbonylamino)-propionamide;
- N-(3-[Cyclopropyl-[6-(2-cyclopropyl-1-cyclopropylmethyl-ethyl)-4-hydroxy-2-oxo-5,6-dihydro-2H-pyran-3-yl]-methyl]-phenyl)-3-indol-1-yl-propionamide;
- 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(1-(tetrahydro-furan-3-ylmethyl)-propyl)-pyran-2-one;
- 6-(1-(5-Chloro-thiophen-2-ylmethyl)-propyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one;
- 3-(Cyclopropyl-phenyl-methyl)-6-(1-(3,5-dimethyl-isoxazol-4-ylmethyl)-propyl)-4-hydroxy-pyran-2-one;
- 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(1-(tetrahydro-furan-2-ylmethyl)-propyl)-pyran-2-one;
- 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(1-thiophen-2-ylmethyl-propyl)-pyran-2-one;
- 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(1-tetrahydro-pyran-4-ylmethyl)-propyl)-pyran-2-one;
- 3-(Cyclopropyl-phenyl-methyl)-6-(1-furan-2-ylmethyl-propyl)-4-hydroxy-pyran-2-one;
- 3-(Cyclopropyl-phenyl-methyl)-6-(1-(1,3)dioxolan-2-ylmethyl-propyl)-4-hydroxy-pyran-2-one;

- 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(1-(tetrahydro-pyran-3-ylmethyl)-propyl)-pyran-2-one;
- 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(1-(tetrahydro-pyran-2-ylmethyl)-propyl)-pyran-2-one;
- 5 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(1-pyridin-2-ylmethyl-propyl)-pyran-2-one;
- 6-(4-Chloro-1-ethyl-butyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one;
- 6-(3-Chloro-1-ethyl-propyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one;
- 3-(Cyclopropyl-phenyl-methyl)-6-[ethyl-3-(tetrahydro-pyran-2-ylloxy)-propyl]-4-hydroxy-pyran-2-one;
- 10 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(1-pyridin-3-ylmethyl-propyl)-pyran-2-one;
- 3-(Cyclopropyl-phenyl-methyl)-6-(1-ethyl-3-thiophen-3-yl-propyl)-4-hydroxy-pyran-2-one;
- 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-[1-(tetrahydro-pyran-3-ylmethyl)-butyl]-pyran-2-one;
- 15 5-Bromo-6-(2-cyclopropyl-cyclopropylmethyl-ethyl)-4-hydroxy-3-(1-phenyl-propyl)-pyran-2-one;
- 3-(1-Benzyl-2-phenyl-ethyl)-6-(2-cyclopropyl-1-cyclopropylmethyl-ethyl)-4-hydroxy-pyran-2-one;
- 6-(2-Cyclopropylmethyl-ethyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one;
- 20 6-(1-Allyl-but-3-enyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one; 3-(Cyclopropyl-phenyl-methyl)-6-(1-ethyl-3-(2-methoxy-ethoxy)-propyl)-4-hydroxy-pyran-2-one;
- 6-(1-Benzyl-3-(2-methoxy-ethoxy)-propyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one;
- 3-(α -Cyclopropyl-*meta*-(benzyloxycarbonylamino)benzyl)-6-(α -ethyl-phenethyl)-4-hydroxy-2H-pyran-2-one;
- 25 3-(α -Cyclopropyl-*meta*-(*tert*-butyloxycarbonylamino)benzyl)-6-(α -cyclopropylmethyl-cyclopropylethyl)-4-hydroxy-2H-pyran-2-one;
- 4-Hydroxy-3-(1-phenyl-propyl)-6-(1-propyl-butyl)-pyran-2-one;
- 4-Hydroxy-3-(1-phenyl-allyl)-6-(1-propyl-butyl)-pyran-2-one;
- 30 3-(5-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-oxo-6H-pyran-2-yl)-propionic acid *tert*-butyl ester;
- 3-(Cyclopropyl-phenyl-methyl)-6-(2-(3,5-dimethyl-isoxazol-4-yl)-ethyl)-4-hydroxy-pyran-2-one;
- 6-(2-(5-*tert*-Butyl-(1,2,4)oxadiazol-3-yl)-ethyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one;
- 35 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(2-phenyl-1-pyridin-2-ylmethyl-ethyl)-pyran-

- 2-one;
- 3-(Cyclopropyl-phenyl-methyl)-6-(2-(1,3)dioxolan-2-yl-ethyl)-4-hydroxy-pyran-2-one;
- 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(4-morpholin-4-yl-butyl)-pyran-2-one;
- 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(2-pyridin-2-yl-ethyl)-pyran-2-one;
- 5 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(2-(2-methyl-thiazol-4-yl)-ethyl)-pyran-2-one;
- 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(2-quinolin-2-yl-ethyl)-pyran-2-one;
- 6-(3-Chloro-propyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one;
- 6-(1-(2-(4-Chloro-phenyl)-thiazol-4-ylmethyl)-propyl)-3-(cyclopropyl-phenyl-methyl)-4-
- 10 hydroxy-pyran-2-one;
- 3-(Cyclopropyl-phenyl-methyl)-6-(3-(1,3)dioxan-2-yl-1-ethyl-propyl)-4-hydroxy-pyran-2-one;
- 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(1-pyridin-4-ylmethyl-propyl)-pyran-2-one;
- 3-(Cyclopropyl-phenyl-methyl)-6-(1-ethyl-3-morpholin-4-yl-3-oxo-propyl)-4-hydroxy-
- 15 pyran-2-one;
- 3-(Cyclopropyl-phenyl-methyl)-6-(1-ethyl-4-morpholin-4-yl-butyl)-4-hydroxy-pyran-2-one;
- 3-(Cyclopropyl-phenyl-methyl)-6-[1-(2,3-dihydro-benzo[1,4]dioxin-2-ylmethyl)-propyl]-4-hydroxy-pyran-2-one;
- 20 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-isobutyl-pyran-2-one;
- Cyclopropyl-phenyl-methyl)-6-[1-(5,6-dihydro-2H-pyran-3-ethyl)-propyl]-4-hydroxy-pyran-2-one;
- 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-5-(2-(2-methoxy-ethoxy)-ethyl)-6-propyl-pyran-2-one;
- 25 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(1-isobutyl-3-methyl-butyl)-pyran-2-one;
- 3-Dicyclopropylmethyl-4-hydroxy-6-phenethyl-pyran-2-one;
- 6-(1-Cyclopropyl-ethyl)-3-dicyclopropylmethyl-4-hydroxy-pyran-2-one;
- 6-(1-Cyclopropyl-1-cyclopropylmethyl-ethyl)-3-dicyclopropylmethyl-4-hydroxy-pyran-2-one;
- 30 6-(1-Cyclohexylmethyl-propyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one;
- 6-(1-Benzyl-propyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one;
- 6-(2-Cyclopropyl-1-cyclopropylmethyl-ethyl)-4-hydroxy-3-(1-phenyl-propyl)-pyran-2-one;
- 6-(1-Benzyl-2-cyclopropyl-ethyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one;
- 6-(2-Cyclopropyl-ethyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one;
- 35 6-(1-Cyclopropylmethyl-propyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one;
- 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(4-phenyl-butyl)-pyran-2-one;

- 3-(Cyclohexyl-cyclopropyl-methyl)-6-(2-cyclopropyl-1-cyclopropylmethyl-ethyl)-4-hydroxy-pyran-2-one;
- 3-(Cyclopropyl-phenyl-methyl)-6-(1-ethyl-4-phenyl-butyl)-4-hydroxy-pyran-2-one;
- 6-(3-Cyclohexyl-propyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one;
- 5 6-(3-Cyclohexyl-1-ethyl-propyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one;
- 6-(2-Cyclopropyl-ethyl)-4-hydroxy-3-(1-phenyl-propyl)-pyran-2-one;
- 6-But-3-enyl-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one;
- 3-(Cyclopropyl-phenyl-methyl)-6-(1-ethyl-3-phenyl-propyl)-4-hydroxy-pyran-2-one;
- 5-Bromo-6-(2-cyclopropyl-ethyl)-4-hydroxy-3-(1-phenyl-propyl)-pyran-2-one;
- 10 6-(1-Benzyl-2-phenyl-ethyl)-4-hydroxy-3-(1-phenyl-propyl)-pyran-2-one;
- 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(3-(2-methoxy-ethoxy)-propyl)-pyran-2-one;
- 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-5-(2-(2-methoxy-ethoxy)-ethyl)-6-(3-(2-methoxy-ethoxy)-pyran-2-one;
- 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-propyl-pyran-2-one;
- 15 5-Bromo-4-hydroxy-6-phenylethyl-3-(1-phenyl-propyl)-pyran-2-one;
- 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(3-(2-methoxy-ethoxy)-ethoxy)-propyl-pyran-2-one;
- 5-Bromo-4-hydroxy-3-(1-phenyl-propyl)-6-propyl-pyran-2-one;
- 3-(Cyclopropyl-phenyl-methyl)-6-(1-ethyl-propyl)-4-hydroxy-5-(2-(2-methoxy-ethoxy)ethyl)-pyran-2-one;
- 20 6-(1-Benzyl-propyl)-5-bromo-4-hydroxy-3-(1-phenyl-propyl)-pyran-2-one;
- 6-(2-Cyclopropyl-1-cyclopropylmethyl-ethyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-5-(2-(2-methoxy-ethoxy)-ethoxy)-ethyl-pyran-2-one;
- 3-(Cyclopropyl-phenyl-methyl)-6-(2-furan-2-yl-2-hydroxy-ethyl)-4-hydroxy-pyran-2-one;
- 25 3-(Cyclopropyl-phenyl-methyl)-4-hydroxy-6-(4,4,4-trifluoro-butyl)-pyran-2-one;
- 6-[2-(1-Cyclohexyl-1H-tetrazol-5-yl)-ethyl]-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-2-one;
- 4-Hydroxy-3-(1-phenyl-propyl)-1-oxa-spiro[5.5]undec-3-ene-2,9-dione monooxime;
- 5,6-Dihydro-4-hydroxy-6-phenyl-6-(phenylmethyl)-3-(1-phenyl-2-propenyl)-2H-pyran-2-one;
- 30 5,6-Dihydro-4-hydroxy-6-phenyl-6-(phenylmethyl)-3-(1-phenylpropyl)-2H-pyran-2-one;
- 3-(1,3-Diphenyl-2-propenyl)-5,6-dihydro-4-hydroxy-6-(2-phenylethyl)-6-propyl-, (E)-2H-pyran-2-one;
- 35 3-(1,3-Diphenyl-2-propyl)-5,6-dihydro-4-hydroxy-6-(2-phenylethyl)-6-propyl-, (E)-2H-pyran-2-one;

- 3-(1,3-Diphenyl-2-propenyl)-5,6-dihydro-4-hydroxy-6-phenyl-6-(phenylmethyl)-2H-pyran-2-one;
- 3-(1,2-Diphenylethenyl)-5,6-dihydro-4-hydroxy-6-(2-phenylethyl)-6-propyl-, (E)-2H-pyran-2-one;
- 5 5,6-Dihydro-4-hydroxy-6-(2-phenylethyl)-3-(1-phenyl-2-propenyl)-6-propyl-2H-pyran-2-one;
- 5,6-Dihydro-4-hydroxy-6-(2-phenylethyl)-3-(1-phenylpropyl)-6-propyl-2H-pyran-2-one;
- 3-(1,3-Diphenyl-2-propenyl)-5,6-dihydro-4-hydroxy-6-(phenylmethyl)-6-propyl-2H-pyran-2-one;
- 10 3-(1,3-Diphenylpropyl)-5,6-dihydro-4-hydroxy-6-(phenylmethyl)-6-propyl-2H-pyran-2-one;
- 4-Hydroxy-3-(1-phenylallyl)-1-oxa-spiro[5.6]-dodec-3-en-2-one;
- 4-Hydroxy-3-(1-phenylallyl)-1-oxa-spiro[5.4]-dec-3-en-2-one;
- 7-Benzyl-4-hydroxy-3-(1-phenylallyl)-1-oxa-spiro[5.5]undec-3-en-2-one;
- 15 4-Hydroxy-3-(1-phenylpropyl)-1-oxa-spiro[5.4]-dec-3-en-2-one;
- 4-Hydroxy-3-(1-phenyl-2-propenyl)-1-oxaspiro[5.7]tridec-3-en-2-one;
- 4-Hydroxy-3-(1-phenylpropyl)-1-oxaspiro[5.7]tridec-3-en-2-one;
- 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(α -ethyl- β -hydroxyphenethyl)-2H-pyran-2-one;
- 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(β -hydroxy-p-methylphenethyl)-2H-pyran-2-one;
- 20 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(β -hydroxy-p-fluorophenethyl)-2H-pyran-2-one;
- 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(β -hydroxy-p-chlorophenethyl)-2H-pyran-2-one;
- 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(β -hydroxy-m-chlorophenethyl)-2H-pyran-2-one;
- 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(β -hydroxy-o-chlorophenethyl)-2H-pyran-2-one;
- 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(2-(furan-3-yl)-2-hydroxyethyl)-2H-pyran-2-one;
- 25 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(2-(thiophen-3-yl)-2-hydroxyethyl)-2H-pyran-2-one;
- 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(α -ethyl-p-fluorophenethyl)-2H-pyran-2-one;
- 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(α -ethyl-p-chlorophenethyl)-2H-pyran-2-one;
- 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(α -ethyl-m-chlorophenethyl)-2H-pyran-2-one;
- 30 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(α -ethyl-o-chlorophenethyl)-2H-pyran-2-one;
- 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(α -ethyl-p-bromophenethyl)-2H-pyran-2-one;
- 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(α -ethyl-m-bromophenethyl)-2H-pyran-2-one;
- 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(α -ethyl-p-trifluoromethylphenethyl)-2H-pyran-2-one;
- one;
- 35 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(α -ethyl-m-trifluoromethylphenethyl)-2H-pyran-2-one;
- one;

- 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(α -ethyl-o-trifluoromethylphenethyl)-2H-pyran-2-one;
- 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(α -ethyl-p-methoxyphenethyl)-2H-pyran-2-one;
- 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(α -ethyl-m-methoxyphenethyl)-2H-pyran-2-one;
- 5 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(p-fluorophenethyl)-2H-pyran-2-one;
- 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(p-chlorophenethyl)-2H-pyran-2-one;
- 3-(α -cyclopropylbenzyl)-4-hydroxy-6-(p-bromophenethyl)-2H-pyran-2-one;
- 3-(Cyclopropylphenylmethyl)-6-[1-ethyl-3-(4-morpholinyl)propyl]-4-hydroxy-2H-pyran-2-one;
- 10 3-(Cyclopropylphenylmethyl)- β -ethyl-4-hydroxy-2-oxo-, phenylmethyl ester 2H-pyran-6-propanoic acid;
- 3-(Cyclopropylphenylmethyl)-4-hydroxy-6-[2-methyl-1-(phenylmethyl)propyl]-2H-pyran-2-one;
- 3-(Cyclopropylphenylmethyl)-4-hydroxy-6-[2-methyl-1-[(tetrahydro-2H-pyran-3-yl)methyl]propyl]-2H-pyran-2-one;
- 15 4-Hydroxy-3-(1-phenylpropyl)-6-[1-[(tetrahydro-2H-pyran-3-yl)methyl]propyl]-2H-pyran-2-one;
- 3-(Cyclopropylphenylmethyl)-6-(1-ethyl-4,4,4-trifluorobutyl)-4-hydroxy-2H-pyran-2-one;
- 3-[2-[3-(Cyclopropylphenylmethyl)-4-hydroxy-2-oxo-2H-pyran-6-yl]butyl]-1-[(4-methylphenyl)sulfonyl]-piperidine;
- 20 2-[2-[3-(Cyclopropylphenylmethyl)-4-hydroxy-2-oxo-2H-pyran-6-yl]butyl]-1-[(4-methylphenyl)sulfonyl]-pyrrolidine;
- 3-(Cyclopropylphenylmethyl)-4-hydroxy-6-(3,3,3-trifluoropropyl)-2H-pyran-2-one;
- 2-[2-[3-(Cyclopropylphenylmethyl)-4-hydroxy-2-oxo-2H-pyran-6-yl]butyl]-1-[(4-methylphenyl)sulfonyl]-piperidine;
- 25 4-[2-[3-(Cyclopropylphenylmethyl)-4-hydroxy-2-oxo-2H-pyran-6-yl]butyl]-1-[(4-methylphenyl)sulfonyl]-piperidine;
- 4-[2-[3-(Cyclopropylphenylmethyl)-4-hydroxy-2-oxo-2H-pyran-6-yl]butyl]-1-(phenylmethyl)-2-pyrrolidinone;
- 30 6-(Cyclopentylmethyl)-3-(cyclopropylphenylmethyl)-4-hydroxy-2H-pyran-2-one;
- 3-(Cyclopropylphenylmethyl)-4-hydroxy-6-[(tetrahydro-2H-pyran-4-yl)methyl]-2H-pyran-2-one;
- 3-(Cyclopropylphenylmethyl)-6-(3-fluoropropyl)-4-hydroxy-2H-pyran-2-one;
- 4-Hydroxy-3-(1-phenylcyclobutyl)-6-[1-(phenylmethyl)propyl]-2H-pyran-2-one;
- 35 3-(α -Ethylbenzyl)-6-(α -ethylbenzyl)-4-hydroxy-2H-pyran-2-one;
- 3-(α -Cyclopropyl-*meta*-(phenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-

- 2H-pyran-2-one;
 3-(α -Cyclopropyl-*meta*-(propylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-
 2H-pyran-2-one;
 3-(α -Cyclopropyl-*meta*-(*E*)-2-phenylethenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-
 5 4-hydroxy-2H-pyran-2-one;
 3-(α -Cyclopropyl-*meta*-(4-bromophenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-
 hydroxy-2H-pyran-2-one;
 3-(α -Cyclopropyl-*meta*-(2,5-dichlorophenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-
 4-hydroxy-2H-pyran-2-one;
 10 3-(α -Cyclopropyl-*meta*-(4-*tert*-butylphenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-
 hydroxy-2H-pyran-2-one;
 3-(α -Cyclopropyl-*meta*-(4-cyanophenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-
 hydroxy-2H-pyran-2-one;
 3-(α -Cyclopropyl-*meta*-(4-methoxyphenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-
 15 hydroxy-2H-pyran-2-one;
 6-Butyl-5,6-dihydro-3-(1,3-diphenyl-2-propenyl)-4-hydroxy-6-phenylmethyl-2H-pyran-2-
 one;
 6-Butyl-5,6-dihydro-3-(1,3-diphenylpropyl)-4-hydroxy-6-phenylmethyl-2H-pyran-2-one;
 6-Butyl-5,6-dihydro-4-hydroxy-6-phenylmethyl-3-(1-phenyl-2-propenyl)-2H-pyran-2-one;
 20 6-Butyl-5,6-dihydro-4-hydroxy-6-phenylmethyl-3-(1-phenylpropyl)-2H-pyran-2-one;
 3-(α -Cyclopropyl-[5-(methoxymethoxy-methyl)-thiophen-2-yl]-methyl)-5,6-dihydro-4-
 hydroxy-6-(2-methylpropyl)-6-(2-phenylethyl)-2H-pyran-2-one;
 5,6-Dihydro-4-hydroxy-6-(2-methylpropyl)-6-(2-phenylethyl)-3-(1-phenyl-2-propenyl)-
 2H-pyran-2-one;
 25 5,6-dihydro-4-hydroxy-6-(2-methylpropyl)-6-(2-phenylethyl)-3-(1-phenylpropyl)-2H-
 pyran-2-one;
 5,6-Dihydro-3-diphenylmethyl-4-hydroxy-6,6-di-(2-phenylethyl)-2H-pyran-2-one;
 5,6-Dihydro-4-hydroxy-6,6-di-(2-phenylethyl)-3-(1,3-diphenyl-2-propenyl)-2H-pyran-2-
 one;
 30 5,6-Dihydro-4-hydroxy-6,6-di-(2-phenylethyl)-3-(1,3-diphenylpropyl)-2H-pyran-2-one;
 5,6-Dihydro-4-hydroxy-3-(1,3-diphenyl-2-propenyl)-6-(3-phenylpropyl)-6-propyl-2H-
 pyran-2-one;
 5,6-Dihydro-4-hydroxy-3-(1,3-diphenylpropyl)-6-(3-phenylpropyl)-6-propyl-2H-pyran-2-
 one;
 35 3-(α -Cyclopropyl-[5-(methoxymethoxy-methyl)-thiophen-2-yl]-methyl)-5,6-dihydro-4-
 hydroxy-6-(2-phenylethyl)-6-propyl-2H-pyran-2-one;

- 3-(α -Cyclopropyl-[5-(methoxymethoxy-methyl)-thiophen-2-yl]-methyl)-5,6-dihydro-4-hydroxy-6-(3-phenylpropyl)-6-propyl-2H-pyran-2-one;
- 5,6-Dihydro-3-diphenylmethyl-4-hydroxy-6-(3-phenylpropyl)-6-propyl-2H-pyran-2-one;
- 3-Diphenylmethyl-5,6-dihydro-4-hydroxy-6-(2-methylpropyl)-6-(2-phenylethyl)-2H-pyran-2-one;
- 3-(1,3-Diphenyl-2-propenyl)-5,6-dihydro-4-hydroxy-6-(2-methylpropyl)-6-(2-phenylethyl)-2H-pyran-2-one;
- 3-(1,3-Diphenyl-2-propyl)-5,6-dihydro-4-hydroxy-6-(2-methylpropyl)-6-(2-phenylethyl)-2H-pyran-2-one;
- 3-(α -Cyclopropyl-*meta*-[(phenylaminocarbonyl)amino]benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 3-(α -Cyclopropyl-*meta*-[(4-methoxyphenylaminocarbonyl)amino]benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 3-(α -Cyclopropyl-*meta*-[(benzylaminocarbonyl)amino]benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 3-(α -Cyclopropyl-*meta*-[(4-bromophenylaminocarbonyl)amino]benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 3-(α -Cyclopropyl-*meta*-[(phenylsulfonylaminocarbonyl)amino]benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 3-(α -Cyclopropyl-*meta*-(*N*- α -*tert*-butyloxycarbonyl-*N*-im-p-toluenesulfonyl-L-histidylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 3-(α -Cyclopropyl-*meta*-(*tert*-butyloxycarbonyl-L-alanyl-amino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 3-(α -Cyclopropyl-*meta*-(4-bromophenylbenzoylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 3-(α -Cyclopropyl-*meta*-(*N*- α -*tert*-butyloxycarbonyl-L-histidylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 3-(α -Cyclopropyl-*meta*-(*N*-benzyloxycarbonyl-O- α -benzyl-L-glutamylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 3-(α -Cyclopropyl-*meta*-(4-cyanophenylbenzoylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 3-(α -Cyclopropyl-*meta*-(L-glutamylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 3-(α -Cyclopropyl-*meta*-(3-(1-indolyl)propanoylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;

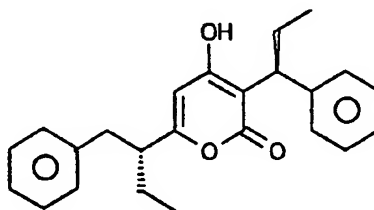
- 3-(α -Cyclopropyl-*meta*-(2-pyridylacetyl-amino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 3-(α -Cyclopropylbenzyl)-6-[1-cyclopropylmethyl-2-(tetrahydropyran-3-yl)ethyl]-4-hydroxy-2H-pyran-2-one;
- 5 3-(α -Cyclopropyl-*meta*-(3-pyridylacetyl-amino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 3-(α -Cyclopropyl-*meta*-(4-pyridylacetyl-amino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 3-(α -Cyclopropyl-*meta*-(4-chlorophenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 10 3-(α -Cyclopropyl-*meta*-(8-quinolinesulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 3-(α -Cyclopropyl-*meta*-(ethylsulfonylamino)benzyl)-6-[1-cyclopropylmethyl-2-(tetrahydropyran-3-yl)ethyl]-4-hydroxy-2H-pyran-2-one;
- 15 3-(α -Cyclopropyl-*meta*-(4-methylphenylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 3-(α -Cyclopropyl-*meta*-(4-methylphenylsulfonylamino)benzyl)-6-[1-cyclopropylmethyl-2-(tetrahydropyran-3-yl)ethyl]-4-hydroxy-2H-pyran-2-one;
- 3-(α -Cyclopropyl-*meta*-(ethylsulfonylamino)benzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 20 (3S,6R) 3-(α -ethylbenzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- (3S,6S) 3-(α -ethylbenzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- Sodium (3S,6R) 3-(α -ethylbenzyl)-6-(α -ethylphenethyl)-2H-pyran-2-one 4-oxide;
- (3R,6R) 3-(α -ethylbenzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one; and
- 25 (3R,6S) 3-(α -ethylbenzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one.
28. The use of claim 26 wherein the compound is selected from the group consisting of:
- 3-(α -Ethylbenzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 6-(1-Benzyl-propyl)-3-(cyclopropyl-phenyl-methyl)-4-hydroxy-pyran-2-one;
- 30 3-(α -Ethylbenzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
- 3-(α -Ethylbenzyl)-6-phenethyl-4-hydroxy-2H-pyran-2-one; and
- 4-Hydroxy-3-(1-phenylpropyl)-6-[(tetrahydro-2H-pyran-3-yl)methyl]propyl]-2H-pyran-2-one.
29. The use of claim 25 wherein the effective amount is from about 100 to 400 mg/kg/day.

-340-

30. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of the compound of claim 1.

31. A process for making a compound of the formula CC-5

5



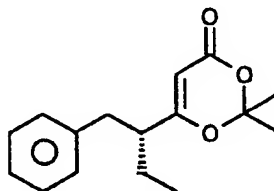
CC-5

10

which comprises:

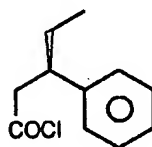
a) reacting a compound of the formula CC-3

15



CC-3

20 with a compound of the formula CC-2

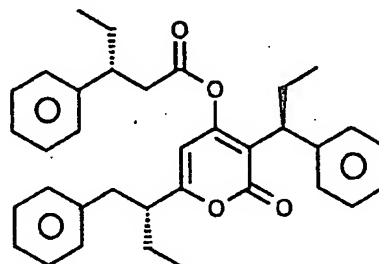


CC-2

25

in a hydrocarbon solvent in the presence of a trialkylamine at an elevated temperature to yield a compound of the formula CC-4

30



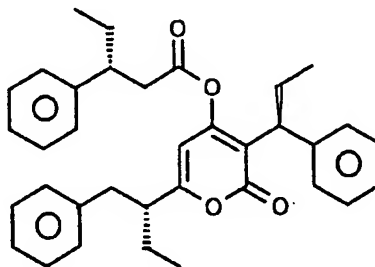
CC-4

35

-341-

- b) treating the compound of formula CC-4 with a base in a water/alcohol mixture;
and
c) treating the mixture of step b) with an acid to yield the compound of formula CC-5.

32. A compound of the formula CC-4



CC-4

33. A compound selected from the group consisting of:

- (3S,6R) 3-(α -ethylbenzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
(3S,6S) 3-(α -ethylbenzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
Sodium (3S,6R) 3-(α -ethylbenzyl)-6-(α -ethylphenethyl)-2H-pyran-2-one 4-oxide;
(3R,6R) 3-(α -ethylbenzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one; and
(3R,6S) 3-(α -ethylbenzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one.

34. The compound of claim 1 selected from the group consisting of:

- (3S,6R) 3-(α -ethyl-4-hydroxybenzyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
(3S,6R) 3-(α -ethylbenzyl)-6-(α -ethyl-4-hydroxyphenethyl)-4-hydroxy-2H-pyran-2-one;
(3S,6R) 3-(α -ethyl-4-hydroxybenzyl)-6-(α -ethyl-4-hydroxyphenethyl)-4-hydroxy-2H-pyran-2-one;
(3S,6 α R,6 β R) 3-(α -ethylbenzyl)-6-(α -ethyl- β -hydroxyphenethyl)-4-hydroxy-2H-pyran-2-one;
(3S,6 α R,6 β S) 3-(α -ethylbenzyl)-6-(α -ethyl- β -hydroxyphenethyl)-4-hydroxy-2H-pyran-2-one;
(3S,6 α R,6 β R) 3-(α -ethyl-4-hydroxybenzyl)-6-(α -ethyl- β -hydroxyphenethyl)-4-hydroxy-2H-pyran-2-one;
(3S,6 α R,6 β S) 3-(α -ethyl-4-hydroxybenzyl)-6-(α -ethyl- β -hydroxyphenethyl)-4-hydroxy-2H-pyran-2-one;
(3S,6 α R,6 β R) 3-(α -ethylbenzyl)-6-(α -ethyl- β -hydroxy-4-hydroxyphenethyl)-4-hydroxy-

- 2H-pyran-2-one;
 (3S,6 α R,6 β S) 3-(α -ethylbenyl)-6-(α -ethyl- β -hydroxy-4-hydroxyphenethyl)-4-hydroxy-
 2H-pyran-2-one;
 (3S,6 α R,6 β R) 3-(α -ethyl-4-hydroxybenyl)-6-(α -ethyl- β -hydroxy-4-hydroxyphenethyl)-4-
 5 hydroxy-2H-pyran-2-one;
 (3S,6 α R,6 β S) 3-(α -ethyl-4-hydroxybenyl)-6-(α -ethyl- β -hydroxy-4-hydroxyphenethyl)-4-
 hydroxy-2H-pyran-2-one;
 (3S,6R) 3-(α -(1[R]-hydroxyethyl)benyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
 (3S,6R) 3-(α -(1[R]-hydroxyethyl)benyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
 10 (3S,6S) 3-(α -ethylbenyl)-6-(α -(1[R]-hydroxyethyl)phenethyl)-4-hydroxy-2H-pyran-2-one;
 (3S,6S) 3-(α -ethylbenyl)-6-(α -(1[S]-hydroxyethyl)phenethyl)-4-hydroxy-2H-pyran-2-one;
 (3S,6S) 3-(α -(1[R]-hydroxyethyl)benyl)-6-(α -(1[R]-hydroxyethyl)phenethyl)-4-hydroxy-
 2H-pyran-2-one;
 (3S,6S) 3-(α -(1[S]ethyl)benyl)-6-(α -(1[S]-hydroxyethyl)phenethyl)-4-hydroxy-2H-pyran-
 15 2-one;
 (3S,6S) 3-(α -(1[R]-hydroxyethyl)benyl)-6-(α -(1[S]-hydroxyethyl)phenethyl)-4-hydroxy-
 2H-pyran-2-one;
 (3S,6S) 3-(α -(1[S]ethyl)benyl)-6-(α -(1[R]-hydroxyethyl)phenethyl)-4-hydroxy-2H-pyran-
 20 2-one;
 (3S,6R) 3-(α -(2-hydroxyethyl)benyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
 (3S,6R) 3-(α -ethylbenyl)-6-(α -(2-hydroxyethyl)phenethyl)-4-hydroxy-2H-pyran-2-one;
 (3S,6R) 3-(α -(2-hydroxyethyl)benyl)-6-(α -(2-hydroxyethyl)phenethyl)-4-hydroxy-2H-
 pyran-2-one;
 3-(α -ethyl-4-hydroxybenyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
 25 3-(α -ethylbenyl)-6-(α -ethyl-4-hydroxyphenethyl)-4-hydroxy-2H-pyran-2-one;
 3-(α -ethyl-4-hydroxybenyl)-6-(α -ethyl-4-hydroxyphenethyl)-4-hydroxy-2H-pyran-2-one;
 3-(α -ethyl-4-hydroxybenyl)-6-(α -ethyl- β -hydroxyphenethyl)-4-hydroxy-2H-pyran-2-one;
 3-(α -ethylbenyl)-6-(α -ethyl- β -hydroxy-4-hydroxyphenethyl)-4-hydroxy-2H-pyran-2-one;
 3-(α -ethyl-4-hydroxybenyl)-6-(α -ethyl- β -hydroxy-4-hydroxyphenethyl)-4-hydroxy-2H-
 30 pyran-2-one;
 3-(α -(1-hydroxyethyl)benyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
 3-(α -ethylbenyl)-6-(α -(1-hydroxyethyl)phenethyl)-4-hydroxy-2H-pyran-2-one;
 3-(α -(1-hydroxyethyl)benyl)-6-(α -(1-hydroxyethyl)phenethyl)-4-hydroxy-2H-pyran-2-
 one;
 35 3-(α -(2-hydroxyethyl)benyl)-6-(α -ethylphenethyl)-4-hydroxy-2H-pyran-2-one;
 3-(α -ethylbenyl)-6-(α -(2-hydroxyethyl)phenethyl)-4-hydroxy-2H-pyran-2-one; and

3-(α -(2-hydroxyethyl)benzyl)-6-(α -(2-hydroxyethyl)phenethyl)-4-hydroxy-2H-pyran-2-one.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 93/10645

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07D309/38 C07D309/32 A61K31/365

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FR,A,1 276 654 (D. MOLHO) 16 October 1961 see page 1 - page 3	1,20,21, 24
A	CHEMICAL ABSTRACTS, vol. 85, no. 27, 1976, Columbus, Ohio, US; abstract no. 78002b, page 533 ; see abstract & CS,A,161 396 (J.VRKOC) 15 November 1975	1,20,21, 24
A	CHEMISCHE BERICHTE vol. 110, no. 3 , 1977 , WEINHEIM DE pages 1047 - 1057 J.-L. FIASSEON 'UBER DIE FARB- UND FLUORECENZSTOFFE DES GRUNBLÄTTRIGEN SCHWEFELKOPFES.' see page 1051 - page 1053; examples 10,16	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

A document member of the same patent family

Date of the actual completion of the international search

11 February 1994

Date of mailing of the international search report

18.02.94

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Francois, J

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 93/10645

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR-A-1276654		NONE	
CS-A-161396		NONE	

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☒ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☒ FADED TEXT OR DRAWING
- ☒ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☒ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☒ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.